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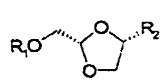
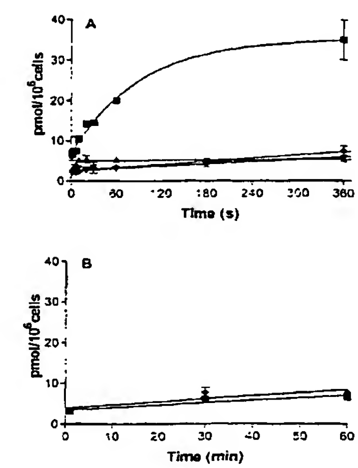
(54) Title: DIOXOLANE ANALOGS FOR IMPROVED INTER-CELLULAR DELIVERY



(I)



(57) Abstract: Compounds having the following formula (I) wherein:R1is, for example, H; C1-24 alkyl; C2-24 alkenyl; C6-24 aryl; C5-20 heteroaromatic ring; or C3-20 non-aromatic ring;R3 and R4 are, for example, in each case independently H; C1-24 alkyl; C2-24 alkenyl; C6-24 aryl; C5-18 heteroaromatic ring; or C3-20 non-aromatic ring; chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R7;R6 is, in each case, H, C1-20 alkyl, C2-20 alkenyl, C0-20 alkyl-C6-24 aryl, C0-20 alkyl-C5-20 heteroaromatic ring, C3-20 non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; and R7 is, in each case, C1-20 alkyl, C2-20 alkenyl, C6-10 aryl, C5-20 heteroaromatic ring, C3-20 non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, -C(O)R6, -C(O)OR6; andX and Y are each independently Br, Cl, I, F, OH, OR3 or NR3R4 and at least one of X and Y is NR3R4; ora pharmaceutically acceptable salt thereof, are useful in treating a patient having cancer.

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DIOXOLANE ANALOGS FOR IMPROVED INTER-CELLULAR DELIVERY

FIELD OF THE INVENTION

The present invention is related to nucleoside analogs for treating cancer, in particular dioxolane nucleoside analogs.

BACKGROUND OF THE INVENTION

Neoplastic diseases, characterized by the proliferation of cells not subject to the normal control of cell growth, are a major cause of death in humans. In the United States only, a total of over about 1 million new cancer cases occurred for the year of 1995 (CA, Cancer J. Clin., 1995:45:8:30) cancer deaths in the United States for 1995 was more than about 500,000.

The usefulness of known cytotoxic agents is compromised by dose limiting toxicities such as myelosuppression as well as the resistance of treated tumors. In view of the proven effectiveness of chemotherapy in the treatment of responsive tumors, efforts have been undertaken to develop novel compounds with either an improved therapeutic index or with reduced cross-resistance.

Antimetabolites, such as nucleoside analogs, have been used in anticancer treatment regimens. Some of the more commonly used analogs include gemcitabine (dFdC), 5-fluorouracil (5-FU), cytosine arabinoside (Ara-C, cytarabine), 6-thioguanine (TG) and 6-mercaptopurine (MP). This class of compounds is generally toxic to

adult tissues that retain a high rate of cell proliferation: bone marrow, intestinal mucosa, hair follicles and gonads.

5-FU is used most commonly in breast and gastrointestinal cancer patients. Major side effects associated with 5-FU administration include bone marrow and mucous membrane toxicities; and minor side effects include skin rashes, conjunctivitis and ataxia. Ara-C, used in the treatment of acute myelocytic leukemia, may cause myelosuppression and gastrointestinal toxicity. TG and MP, used primarily in leukemia patients and rarely in solid tumors, are associated with toxicities similar to that of Ara-C.

β-D-ddC has been investigated by Scanlon et al. in circumvention of human tumor drug resistance (WO 91/07180). Human leukemia cells resistant to cisplatin have shown enhanced sensitivity to β-D-ddC. However, β-D-ddC has been linked to the development of peripheral neuropathy (Yarchoan, et al, Lancet, i:76, 1988) and therefore exhibits in vivo toxicity.

More recently, β-L-Dioxolane cytidine (troxacitabine) was reported to demonstrate anticancer activity (Grove et al. Cancer Research 55, 3008-3011, July 15 1995).

There is therefore a need for anticancer agents that are easy to synthesize and display an improved therapeutic index and efficacy against refractory tumors.

SUMMARY OF THE INVENTION

It is known that gemcitabine and cytarabine enter cancer cells by nucleoside or nucleobase transporter proteins. Mackey et al., *supra*; White et al. (1987). *J. Clin. Investig.* 79, 380-387; Wiley et al. (1982); *J. Clin. Investig.* 69, 479-489; and Gati et al. (1997), *Blood* 90, 346-353. Further, it has been reported that troxacitabine also enters cancer cells by way of nucleoside or nucleobase transporter proteins (NTs). [Grove et al., *Cancer Research* (56), p. 4187-91 (1996)] However, recent studies show that troxacitabine actually enters cancer cells predominately by the mechanism of passive diffusion, rather than by nucleoside transporters. Cytarabine may also enter cells by passive diffusion, but only during a high-dose therapy regimen.

Also, resistance of cancer cells to treatment by anticancer agents has been linked to a deficiency of nucleoside or nucleobase transporter proteins in the cancer cells. (Mackey et al. (1998), *supra*; Mackey et al. (1998b). *Drug Resistance Updates* 1, 310-324; Ullman et al. (1988), *J. Biol. Chem.* 263, 12391-12396; and references cited above.

Thus, in accordance with the invention, cancer treatments are provided in which the anticancer agents utilized enter cells by mechanisms other than through the use of nucleoside or nucleobase transporter proteins, particularly by passive diffusion. Transport through the cell membrane is facilitated by the presence of lipophilic structures. Thus, in

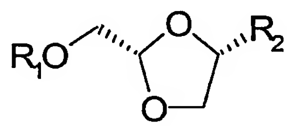
accordance with the invention, entry of anticancer agents into cancer cells by passive diffusion is enhanced by providing the agents with lipophilic structures.

Further, in accordance with the invention, patients with cancers resistant to agents that are transported by nucleoside or nucleobase transporter proteins can be treated with anticancer agents that enter the cells predominately by passive diffusion.

Further, in accordance with the invention, patients with cancers resistant to agents that are transported by nucleoside or nucleobase transporter proteins can be treated with dosages of anticancer agents that increase the entry into the cells by passive diffusion.

In accordance with another aspect of the invention, there is provided a method of treating a patient having a cancer which is resistant to gemcitabine, cytarabine, and/or troxacitabine, by administering to the patient an anticancer agent, for example, a gemcitabine, cytarabine or troxacitabine derivative, that possesses a lipophilic structure to facilitate entry thereof into the cancer cells, particularly by passive diffusion. In accordance with another aspect of the invention, there is provided a method of treating a patient having a cancer, which is resistant to troxacitabine because of poor uptake, by administering an anticancer agent, for example, a troxacitabine derivative, which has a greater lipophilicity than troxacitabine.

According to a further aspect of the invention, there is provided a method for treating a patient having a cancer that is resistant to gemcitabine and/or cytarabine comprising administering to said patient a dioxolane nucleoside compound of the following formula (I):



(I)

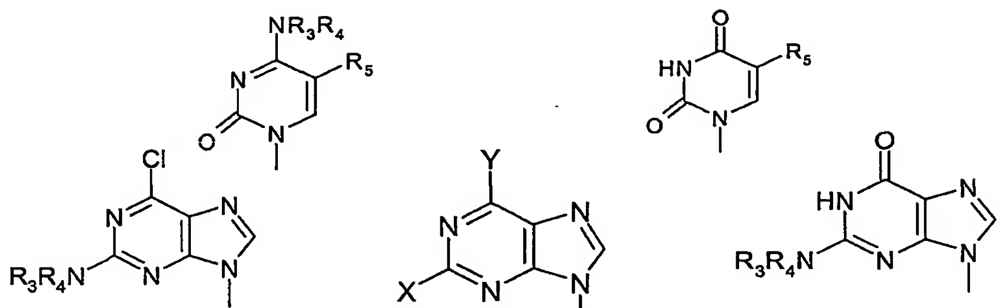
wherein:

R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; trityl; C_{6-24}-aryl-C_{1-24}-alkyl; C_{6-24}-aryl-C_{2-24}-alkenyl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof, wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln (the amino acid chain preferably contains at least one amino acid other than Gly), and which in each case is optionally terminated by -R_7;

R_1 can also be a P(O)(OR')$_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, or C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{6-24}-aryl-C_{1-24}-alkyl; C_{6-24}-aryl-C_{2-24}-alkenyl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6 or an amino acid radical or a dipeptide or tripeptide chain or mimetics thereof, wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln (the amino acid chain preferably contains at least one amino acid other than Gly), and which in each case is optionally terminated by -R_7;

R_3 and R_4 together can also be =CH-N(C_{1-4}-alkyl)$_2$;

R_6 is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-24} alkyl, -C_{6-24} aryl, C_{6-24}-aryl-C_{1-24}-alkyl; C_{6-24}-aryl-C_{2-24}-alkenyl; C_{0-24} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{6-24}-aryl-C_{1-24}-alkyl; C_{6-24}-aryl-C_{2-24}-alkenyl;

C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$ or $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

a pharmaceutically acceptable salt thereof.

The alkyl groups, including alkylene structures, can be straight chain or branched . In addition, within the alkyl or alkylene groups, one or more CH_2 can be replaced, in each case independently, by -O-, -CO-, -S-, $-SO_2-$, -NH-, $-N(C_{1-4}$-alkyl)-, $-N(C_{6-10}$-aryl)-, -CS-, -C=NH-, or $-N(CO-O-C_{1-4}$-alkyl)-, in manner in which O atoms are not directly bonded to one another. In addition, one or more $-CH_2\ CH_2-$ can be replaced, in each case independently, by -CH=CH- or $-C\equiv C-$. Further, alkyl and alkenyl groups can be optionally substituted by halogen, e.g., Cl and F.

Aryl can be unsubstituted or optionally substituted by one or more of NO_2, C_{1-8}-alkyl, C_{1-8}-alkoxy, -COOH, -CO-O-C_{1-8}-alkyl and halo (e.g. Cl and F) groups.

The non-aromatic C_{3-20} groups, which optionally contain 1-3 heteroatoms, are unsubstituted or optionally substituted by one or more of C_{1-8}-alkyl, C_{1-8}-alkoxy, OH, C_{1-8}-hydroxyalkyl, and -CO-O-C_{1-8}-alkyl groups.

According to a further aspect of the invention, there is provided a method for treating a patient having a cancer that is resistant to gemcitabine, cytarabine and/or troxacitabine comprising administering to the

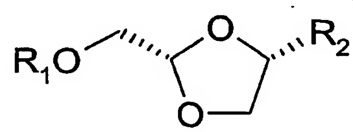
patient a compound according to formula (I) wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$ or $-C(O)OR_6$, then R_6 is other than H.

According to a further aspect of the invention, there is provided a method of treating a patient with cancer, wherein the cancer cells are deficient in one or more nucleoside or nucleobase transporter proteins, comprising administering to the patient a compound according to formula (I). According to a further aspect of the invention, there is provided a method for treating a patient with cancer, wherein the cancer cells are deficient in nucleoside or nucleobase transporter proteins, comprising administering to the patient a compound according to formula (I), wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$ or $-C(O)OR_6$, then R_6 is other than H.

In accordance with another aspect of the invention, there is provided a method for treating a patient with cancer, comprising determining that a compound enters cancer cells predominately by passive diffusion, and administering the compound to the patient, wherein the compound is a compound according to the formula (I). In accordance with another aspect of the invention, there is provided a method for treating a patient with cancer, comprising administering to the patient a compound which has been determined to enter cancer cells predominately by passive diffusion, wherein the compound is in accordance with formula (I). In accordance with a further aspect of the invention,

there is provided a method of treating a patient with cancer, comprising determining that a compound does not enter cancer cells predominately by nucleoside or nucleobase transporter proteins, and administering the compound to the patient, wherein the compound is a compound according to the formula (I).

In accordance with an additional aspect of the invention there are provided anticancer compounds having lipophilic structures, wherein the compounds are of the following formula (I'):



(I')

wherein:

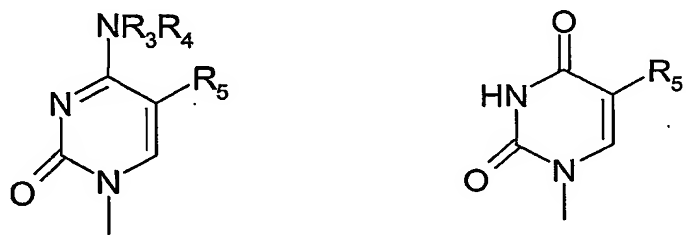
R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof, wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln (the amino acid chain preferably contains at least one amino acid other than Gly), and which in each case is optionally terminated by $-R_7$;

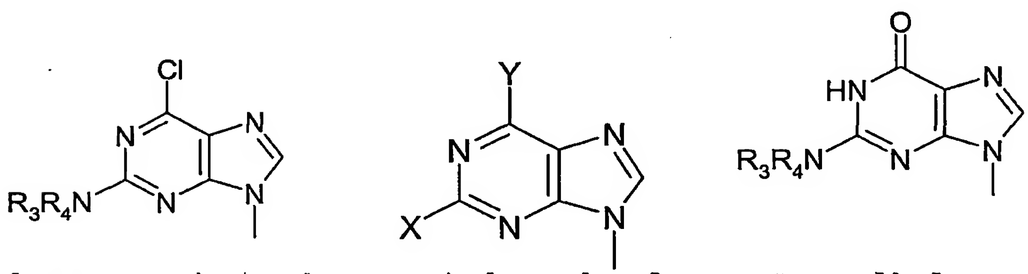
R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18}

acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, or C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is





R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$ or an amino acid radical or a dipeptide or tripeptide chain or mimetics thereof, wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln (the amino acid chain preferably contains at least one amino acid other than Gly), and

which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$ or $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

a pharmaceutically acceptable salt thereof.

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

a pharmaceutically acceptable salt thereof;

with the proviso that at least one of R_1, R_3 and R_4 is

C_{7-20} alkyl;

C_{7-20} alkenyl;

C_{6-24} aryl;

C_{5-20} heteroaromatic ring;

C_{4-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S;

$-C(O)R_6$ in which R_6 is , C_{7-20} alkyl, C_{7-20} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20}

alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S ;

-C(O)OR$_6$ in which R_6 is C_{7-20} alkyl, C_{7-20} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; or

a dipeptide or tripeptide or mimetic thereof where the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln (and the amino acid chain preferably contains at least one amino acid other than Gly), and which is optionally terminated by -R_7.

In an embodiment of the present invention, the R_6 group is connected to the rest of the molecule at a tertiary or quaternary carbon. A tertiary carbon is defined as a carbon atom which has only one hydrogen atom directly attached to it. A quaternary carbon is defined as a carbon atom with no hydrogen atoms attached to it.

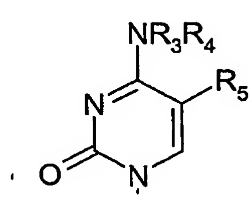
In an alternate embodiment of the present invention, the R_6 group is selected as to provide steric hindrance in the vicinity of the carbonyl group.

Upon further study of the specification and claims, further aspects and advantages of the invention will become apparent to those skilled in the art.

As mentioned above, recent studies have shown that troxacitabine, a L-nucleoside analog, enters cancer cells predominately by passive diffusion, rather than by nucleoside or nucleobase transporter proteins. While this invention is not intended to be limited by any theoretical explanation, it is believed that this property of troxacitabine is at least in part attributed to the dioxolane structure. Further, due to its L-configuration, troxacitabine is a poor substrate for deoxycytidine deaminase. (Grove et al. (1995), *Cancer Res.* 55, 3008-3011) Formula (I) encompasses compounds which are nucleoside analogs having a dioxolane structure and which exhibit the L-configuration. In addition, formula (I) encompasses compounds which exhibit a lipophilic structure. In the case of compounds encompassed by formula (I), the lipophilic structures are provided through modification of the hydroxymethyl structure of the dioxolane sugar moiety and/or modification of amino groups of the base moiety.

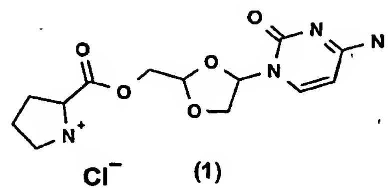
In the compounds of formula (I), preferably at least one of R^1, R^3 and R^4 provides a lipophilic structure. Thus, preferably at least one of R^1, R^3 and R^4 is other than H and, if R^3 and R^4 are each H and R^1 is $C(O)R^6$, $C(O)OR^6$ or $C(O)NHR^6$ then R^6 is other than H.

R^2 is preferably a cytosine base structure, as in the case of troxacitabine. In particular, R^2 is preferably



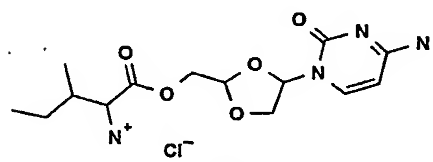
The following are examples of compounds in accordance with the invention:

COMPOUND #1



(1)

COMPOUND #2



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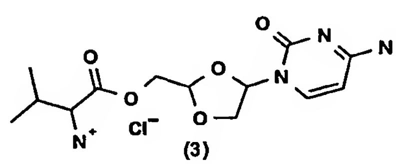
COMPOUND #3



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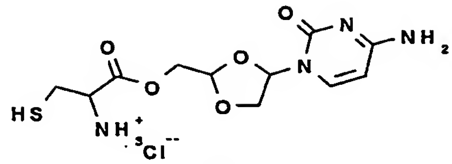
COMPOUND #4



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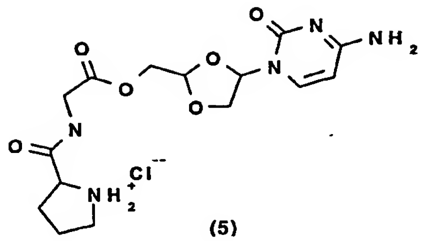
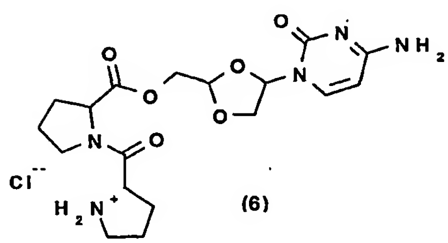
COMPOUND #5



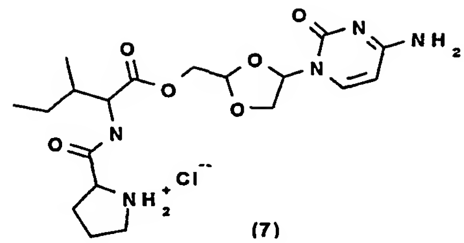
(5)

COMPOUND #6



(6)

COMPOUND #7



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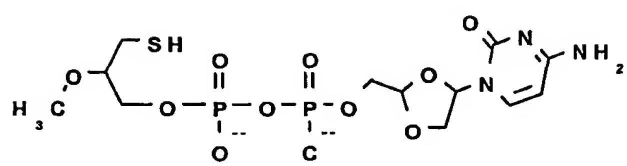
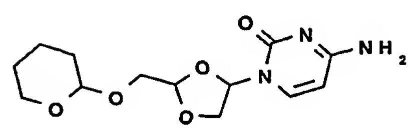
COMPOUND #8



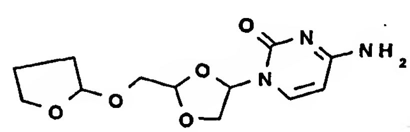
(8)

COMPOUND #9



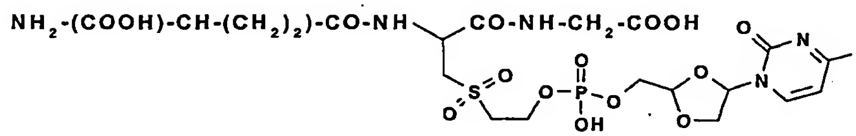
(9)

COMPOUND #10



(10)

COMPOUND #11



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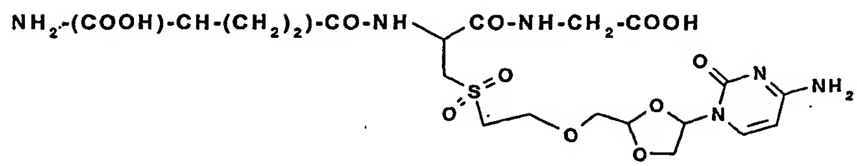

(12)

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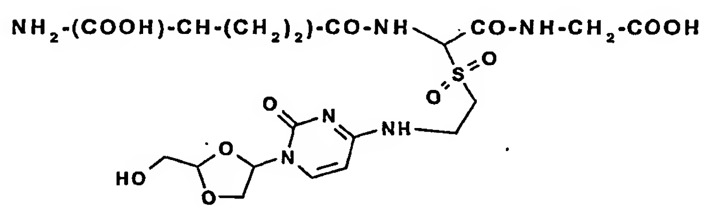

(13)

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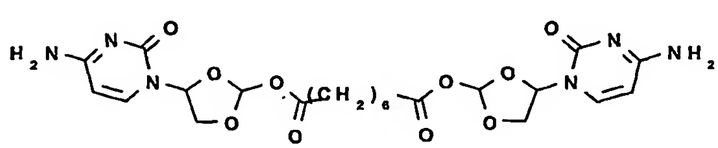
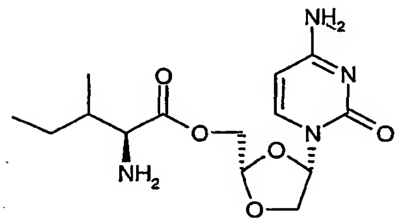


(14)

COMPOUND #15



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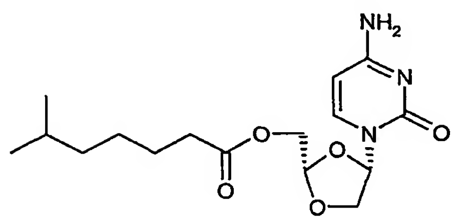

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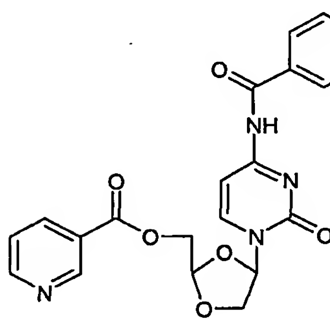

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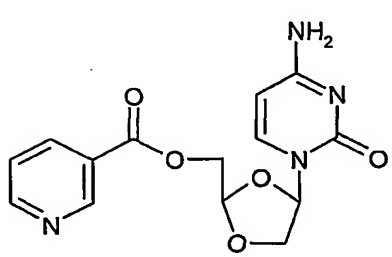

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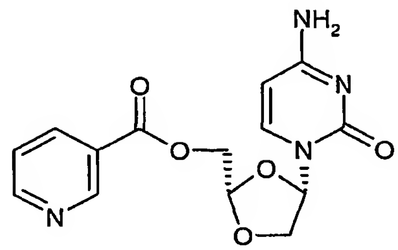

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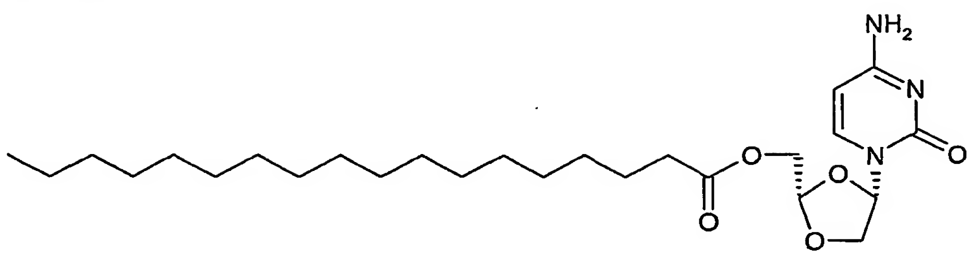

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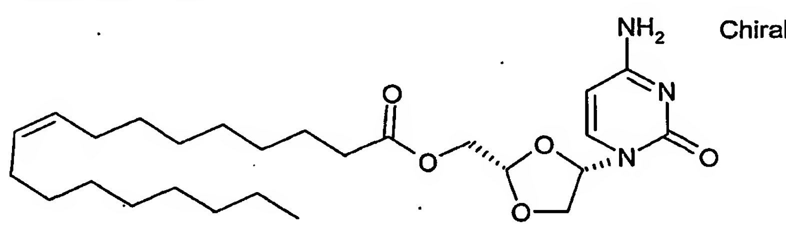

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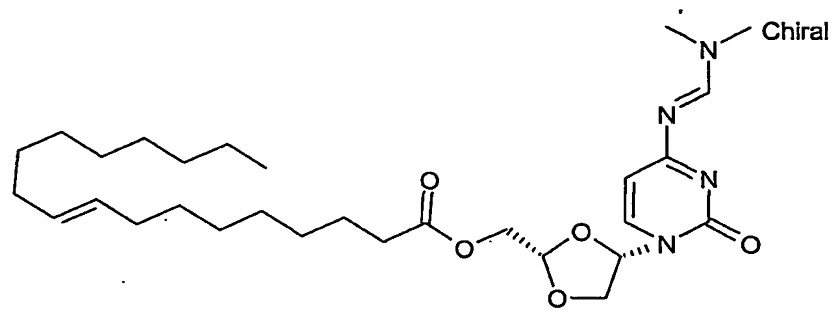

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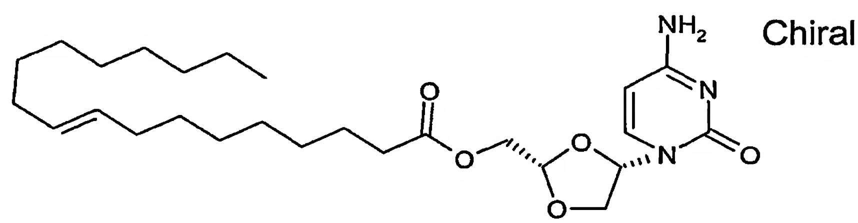

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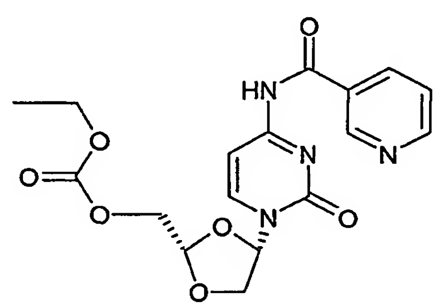

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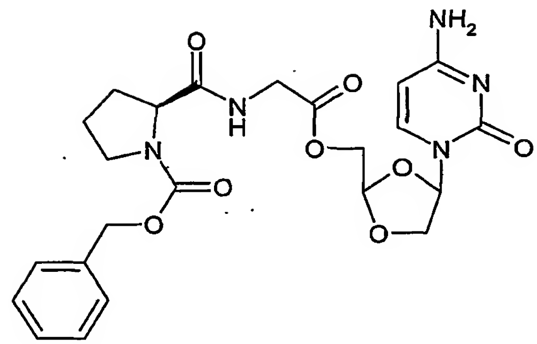

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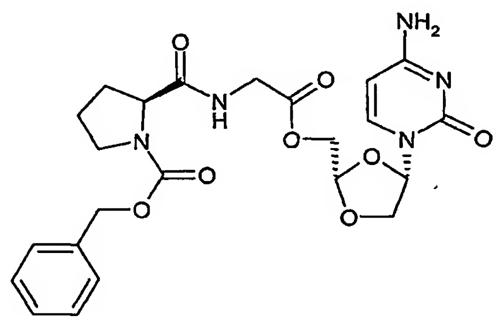

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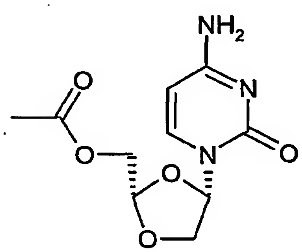

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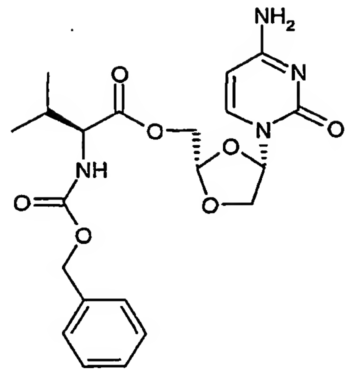

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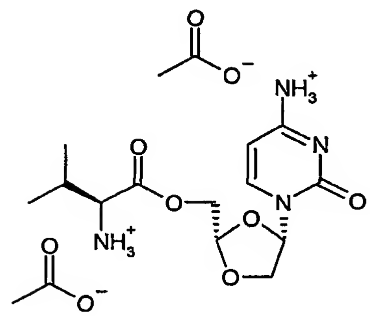

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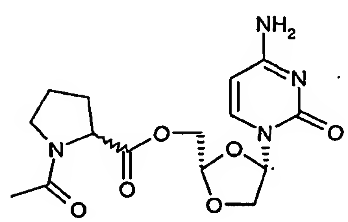

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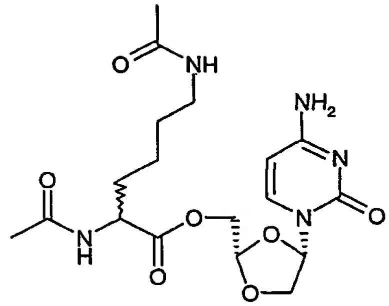

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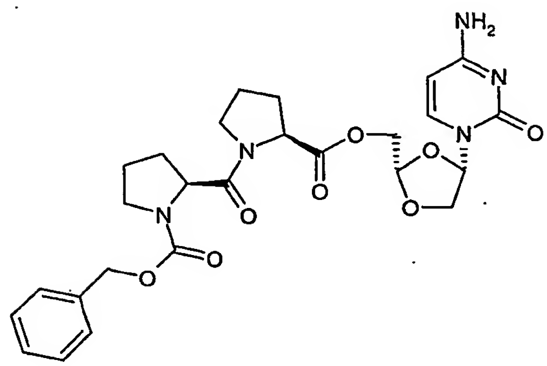

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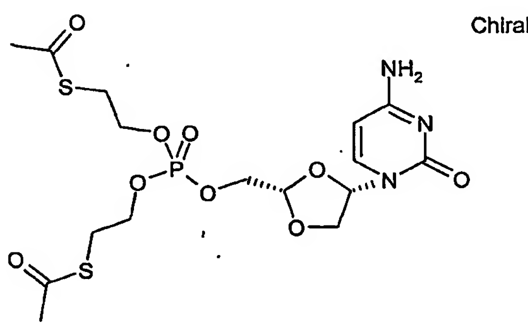

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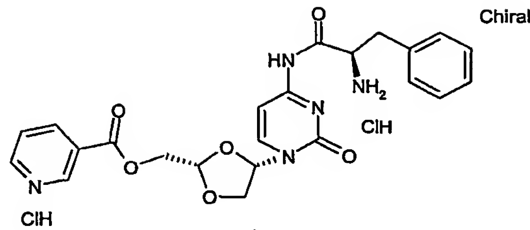

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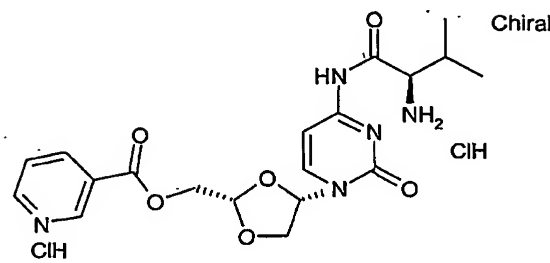

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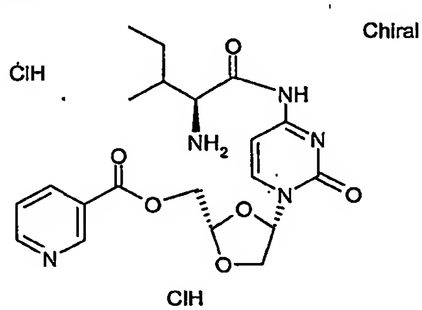

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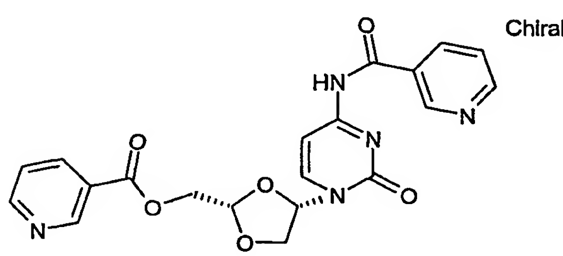
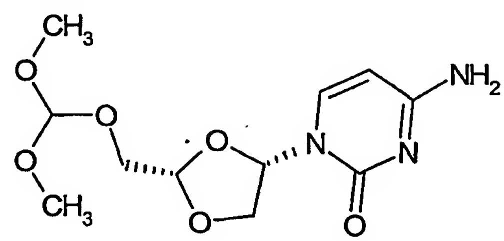
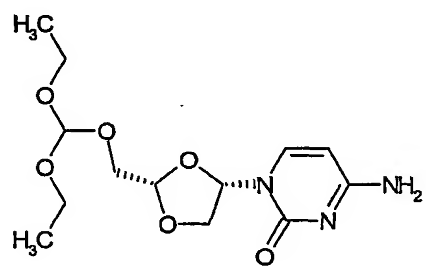
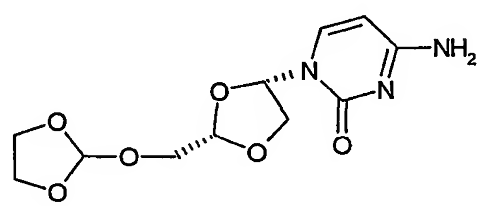
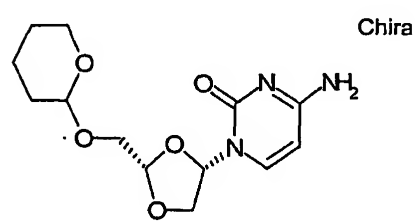
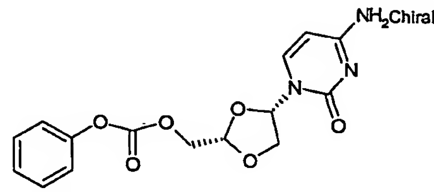
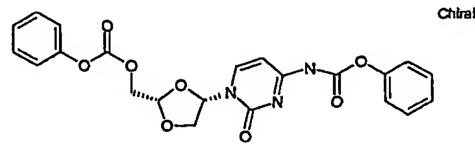
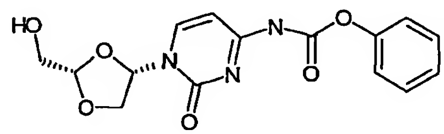
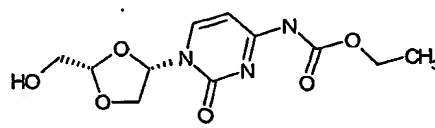
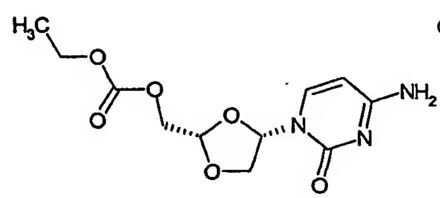
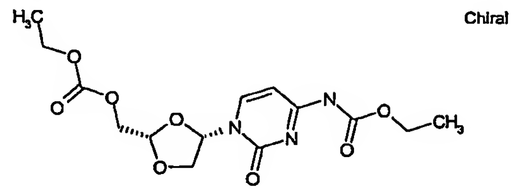
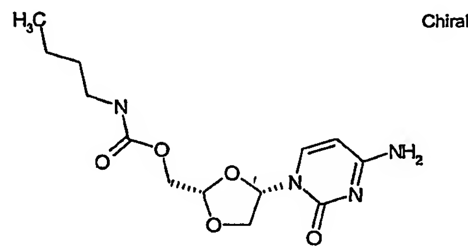
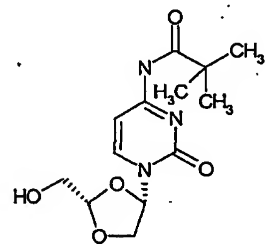
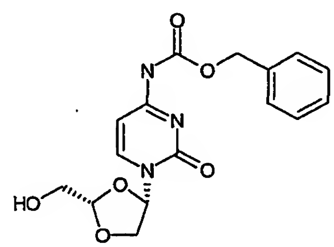
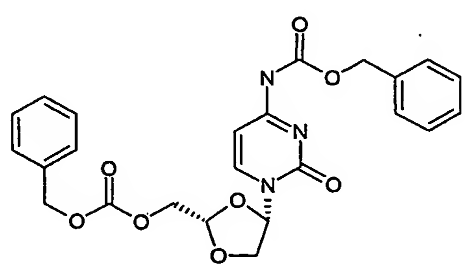
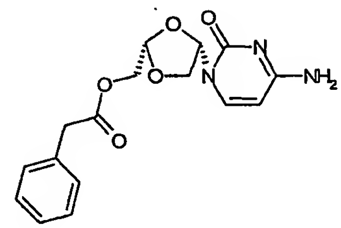
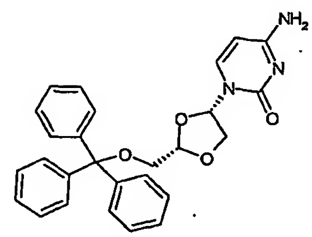
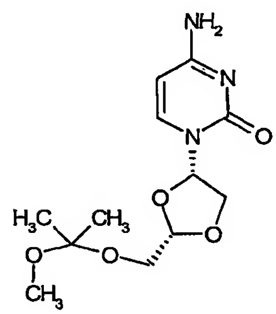
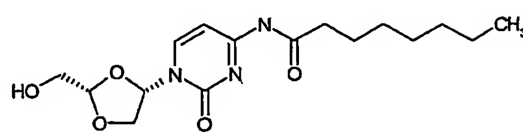
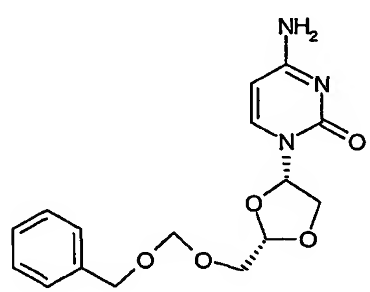


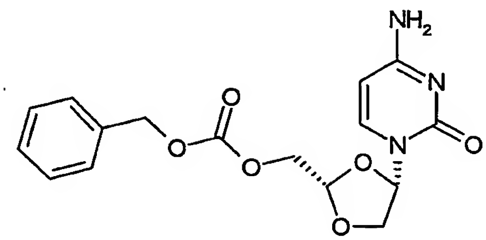
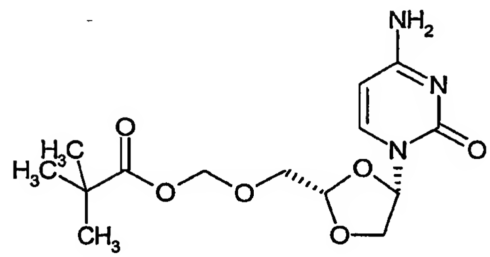
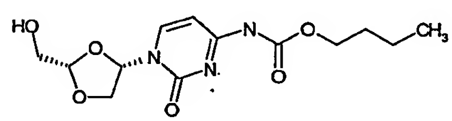
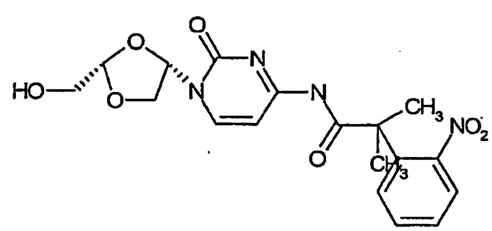
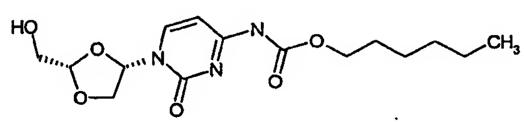
The following compounds 38 to 281 are also compounds in accordance with the invention:

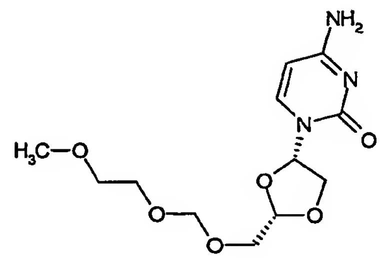
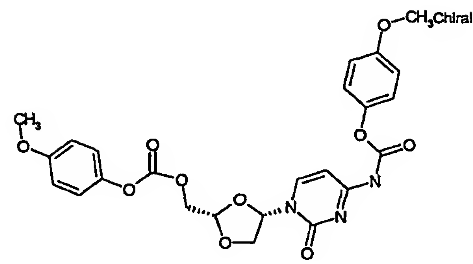
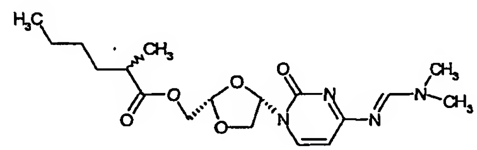
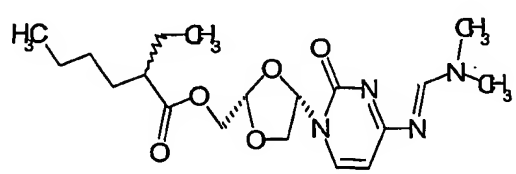
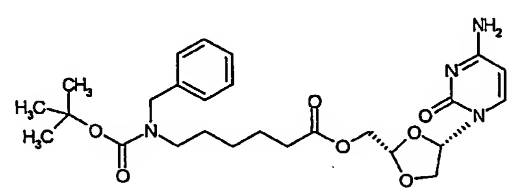
No.	Name	Structure
38	4-AMINO-1-(2-DIMETHOXYMETHOXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	
39	4-AMINO-1-(2-DIETHOXYMETHOXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	
40	4-AMINO-1-[2-([1,3]DIOXOLAN-2-YLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
41	4-AMINO-1-[2-(TETRAHYDRO-PYRAN-2-YLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	

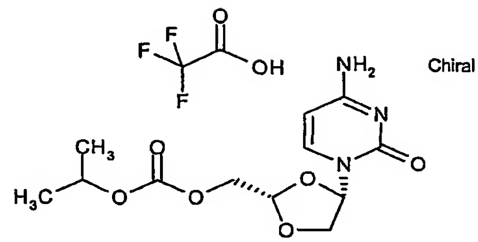
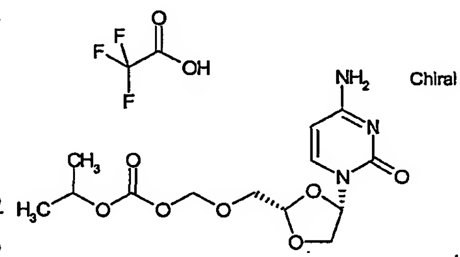
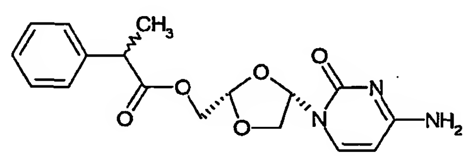
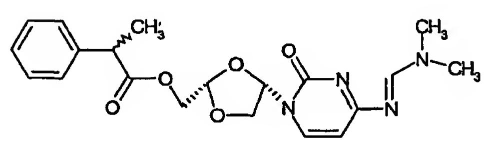
No.	Name	Structure
42	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER PHENYL ESTER	
43	CARBONIC ACID 4-(2-OXO-4-PHENOXYCARBONYLAMINO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER PHENYL ESTER	
44	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID PHENYL ESTER	
45	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID ETHYL ESTER	
46	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER ETHYL ESTER	

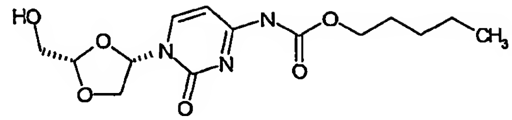
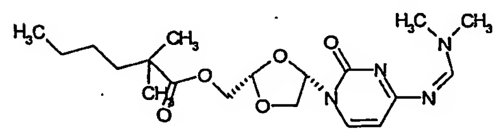
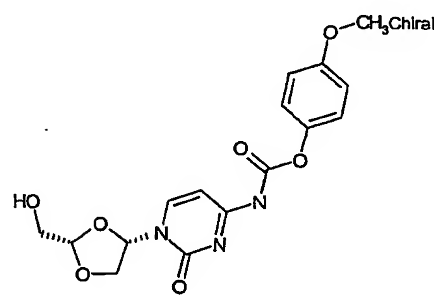
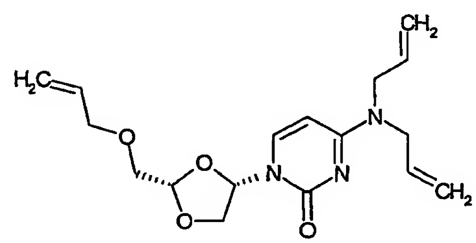
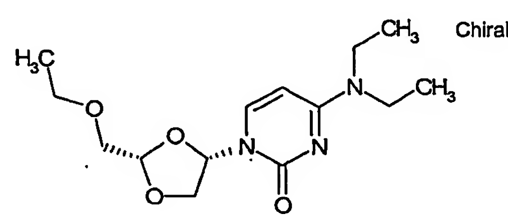
No.	Name	Structure
47	CARBONIC ACID 4-(4-ETHOXYCARBONYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER ETHYL ESTER	
48	BUTYL-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
49	N-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-CYTOSYL]-2,2-DIMETHYL-PROPIONAMIDE	
50	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-CYTOSYL]-CARBAMIC ACID BENZYL ESTER	
51	4-(4-BENZYLOXYCARBONYLAMINOCYTOSYL)-[1,3]DIOXOLAN-2-YLMETHYL BENZYL CARBONATE	

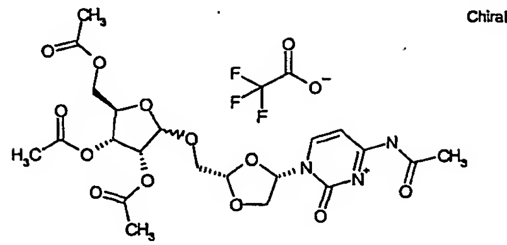
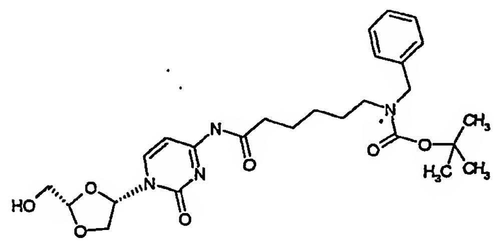
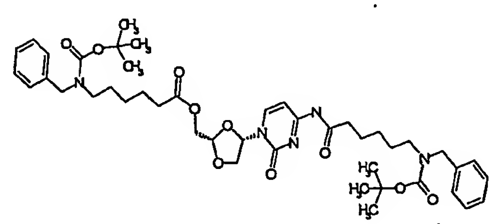
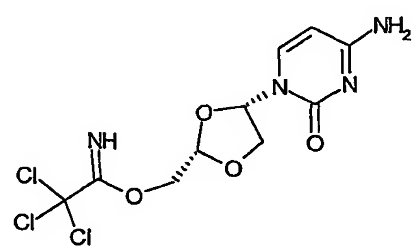
No.	Name	Structure
52	(2S,4S)-2-PHENYLACETOXYMETHYL-4-CYTOSIN-1'-YL-1,3-DIOXOLANE	
53	4-AMINO-1-(2-TRITYLOXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	
54	4-AMINO-1-[2-(1-METHOXY-1-METHYL-ETHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
55	OCTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
56	4-AMINO-1-(2-BENZYLOXYMETHOXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	

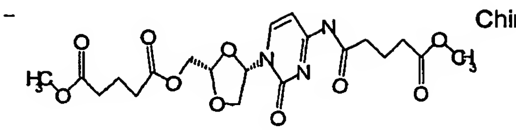
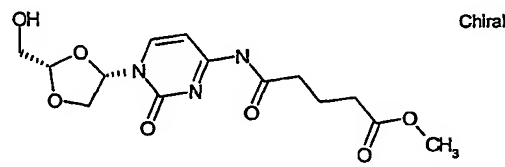
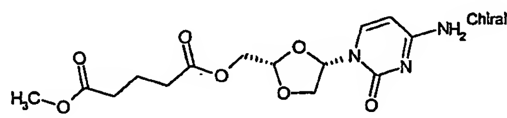
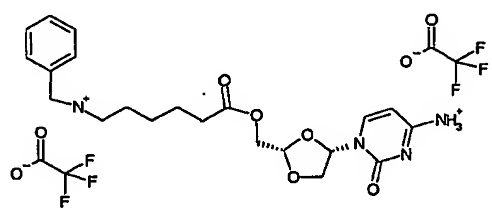
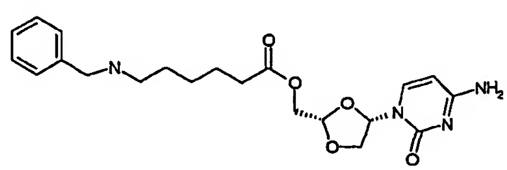
No.	Name	Structure
57	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER BENZYL ESTER	
58	2,2-DIMETHYL-PROPIONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHOXYMETHYL ESTER	
59	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID BUTYL ESTER	
60	(2S,4S)--2-HYDROXYMETHYL-4-N-[2''-(2'''-NITROPHENYL)-2''-METHYLPROPIONYL]-CYTOSINE-1'-YL-1,3-DIOXOLANE	
61	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID HEXYL ESTER	

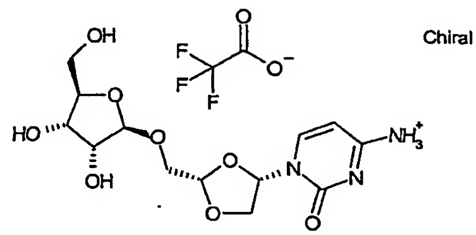
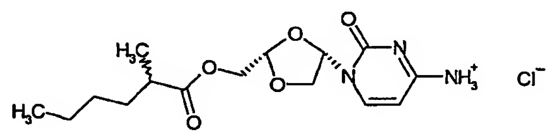
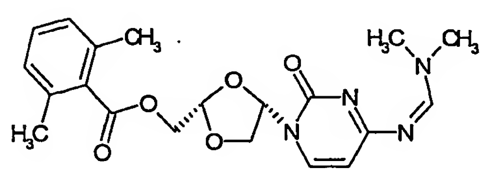
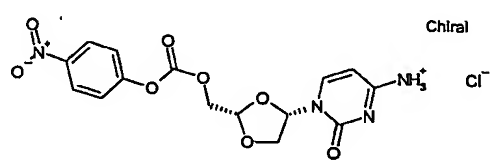
No.	Name	Structure
62	4-AMINO-1-[2-(2-METHOXY-ETHOXYMETHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
63	CARBONIC ACID 4-[4-(4-METHOXY-PHENOXYCARBONYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-METHOXY-PHENYL ESTER	
64	(2S,4S)-2-(2''-METHYL-HEXANOICOXYMETHYL)-4-(4'-NN-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
65	(2S,4S)-2-(2''-ETHYL-HEXANOICOXYMETHYL)-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
66	6-(Benzyl-tert-butoxycarbonyl-amino)-hexanoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester	

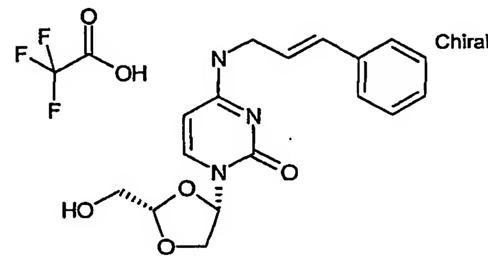
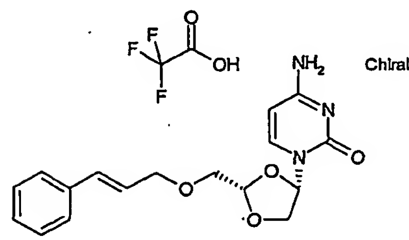
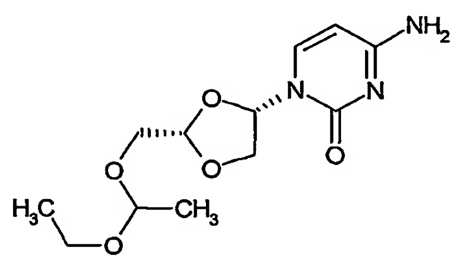
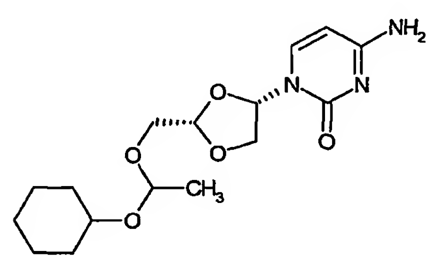
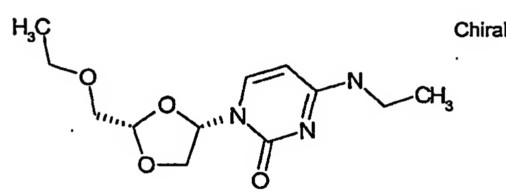
No.	Name	Structure
67	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER ISOPROPYL ESTER TRIFLUOROACETATE SALT	
68	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHOXYMETHYL ESTER ISOPROPYL ESTER TRIFLUOROACETIC ACID SALT	
69	(2S,4S)-2-(2''-METHYLPHENYLACETOXY)METHYL-4-CYTOSIN-1'-YL-1,3-DIOXOLANE	
70	(2S,4S)-2-(2''-METHYLPHENYLACETOXY)METHYL-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	

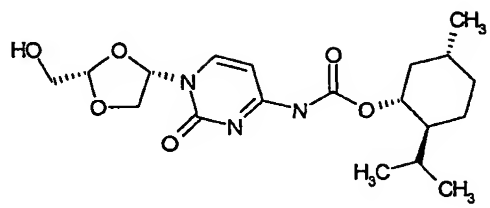
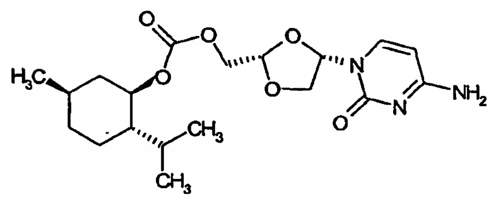
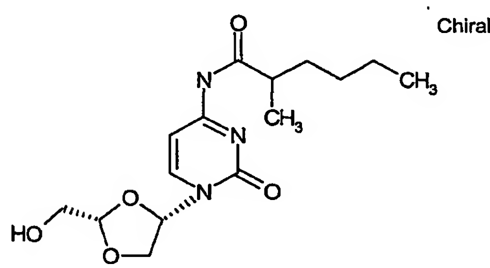
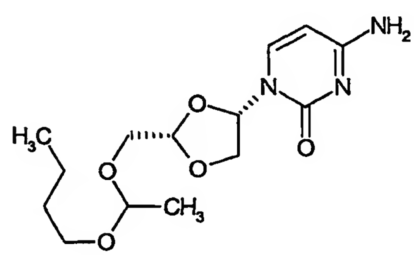
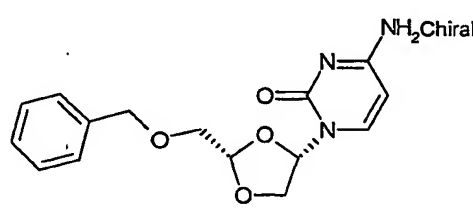
No.	Name	Structure
71	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID PENTYL ESTER	
72	(2S,4S)-2-(2''-DIMETHYLHEXANOICOXYMETHYL)-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
73	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 4-METHOXY-PHENYL ESTER	
74	1-(2-ALLYLOXYMETHYL-[1,3]DIOXOLAN-4-YL)-4-AMINO-1H-PYRIMIDIN-2-ONE	
75	4-AMINO-1-(2(S)-ETHOXYMETHYL-[1,3]DIOXOLAN-4(S)-YL)-1H-PYRIMIDIN-2-ONE	

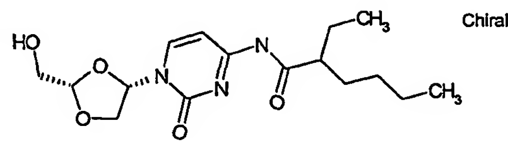
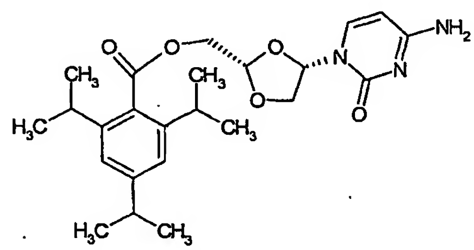
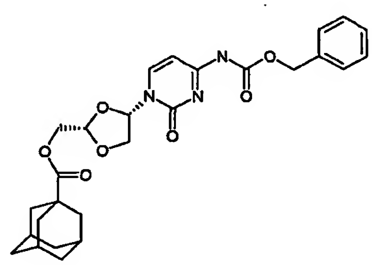
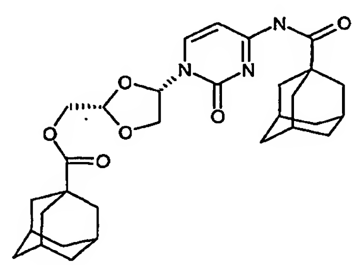
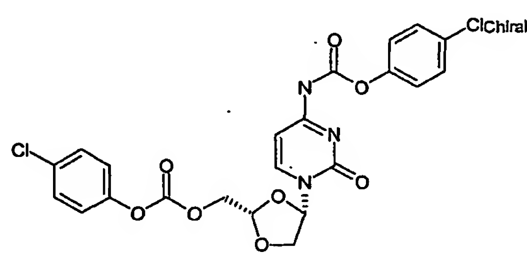
No.	Name	Structure
76	N-[1-(2(S)-D-RIBOSYLOXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-ACETAMIDE	
77	Benzyl-{5-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-ylcarbamoyl]-pentyl}-carbamic acid tert-butyl ester	
78	6-(Benzyl-tert-butoxycarbonyl-amino)-hexanoic acid 4-{4-[6-(benzyl-tert-butoxycarbonyl-amino)-hexanoylamino]-2-oxo-2H-pyrimidin-1-yl}-[1,3]dioxolan-2-ylmethyl ester	
79	2,2,2-TRICHLORO-ACETIMIDIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	

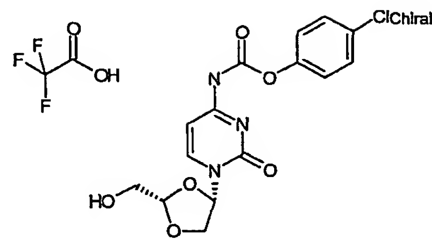
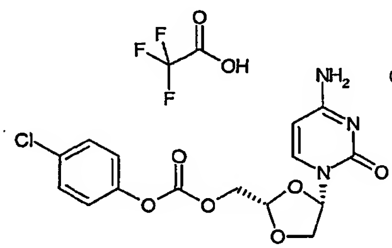
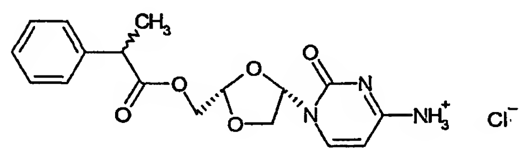
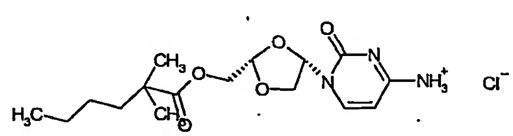
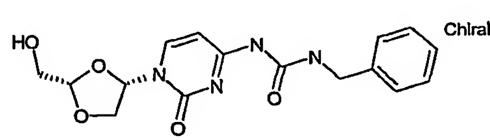
No.	Name	Structure
80	PENTANEDIOIC ACID 4-[4-(4-METHOXYCARBONYL-BUTYRYLAMINO)-2-OXO-2#H!-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER METHYL ESTER	
81	4-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYL]-BUTYRIC ACID METHYL ESTER	
82	PENTANEDIOIC ACID 4-(4-AMINO-2-OXO-2#H!-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER METHYL ESTER	
83	6-Benzylamino-hexanoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester bis trifluoroacetate salt	
84	6-Benzylamino-hexanoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester	

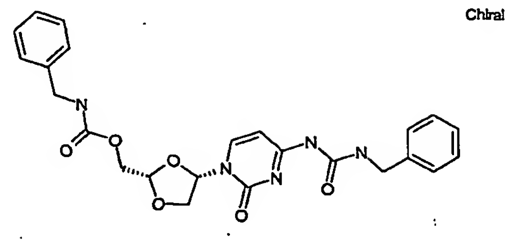
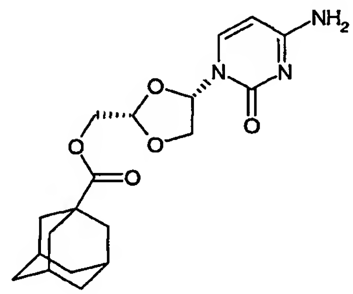
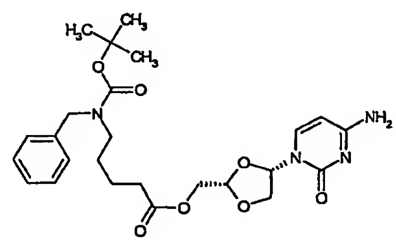
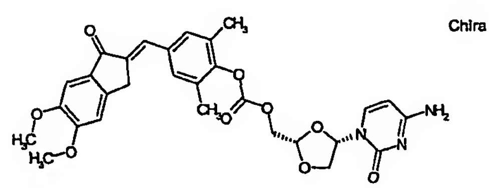
No.	Name	Structure
85	4-AMINO-1-[2-(3,4-DIHYDROXY-5-HYDROXYMETHYL-TETRAHYDROFURAN-2-YLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1HPYIMIDIN-2-ONE, TRIFLUOROACETIC ACID SALT	
86	(2S,4S)-2-(2"-METHYL-HEXANOICOXYMETHYL)-4-CYTOSIN-1'-YL-1,3-DIOXOLANE HYDROCHLORIDE	
87	(2S,4S)-2-(2",6"-DIMETHYLBENZOYLOXYMETHYL)-4-(4'-N,N-DIMETHYLAMINOMETHLYENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
88	1-[2-(4-NITRO-PHENOXYCARBONYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL-AMMONIUM; CHLORIDE	

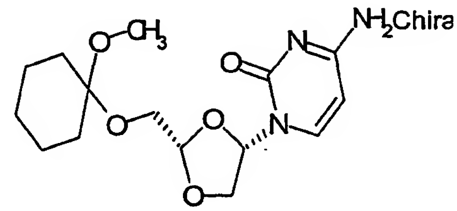
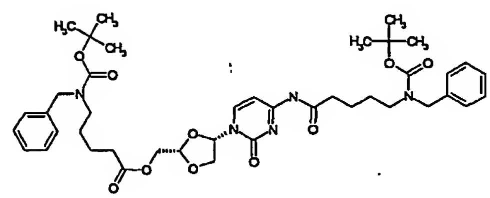
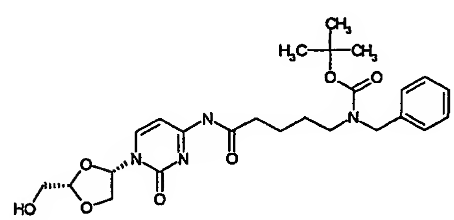
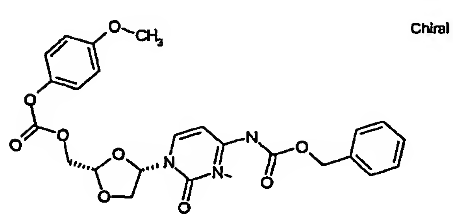
No.	Name	Structure
89	1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-4-(3-CINNAMYL)-1H-PYRIMIDIN-2-ONE TRIFLUORO-ACETATE SALT	
90	4-AMINO-1-[2-(3-CINNAMYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE TRIFLUOROACETATE SALT	
91	4-AMINO-1-[2-(1-ETHOXY-ETHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
92	4-AMINO-1-[2-(1-CYCLOHEXYLOXY-ETHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
93	1-(2'(S)-ETHOXYMETHYL-[1,3]DIOXOLAN-4'(S)-YL)-4-ETHYLAMINO-1H-PYRIMIDIN-2-ONE	

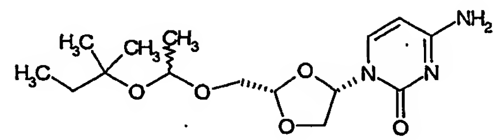
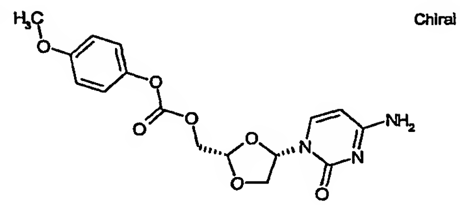
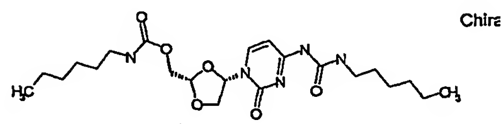
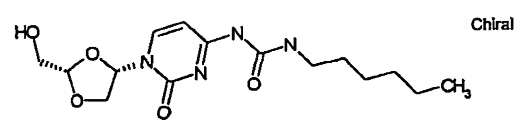
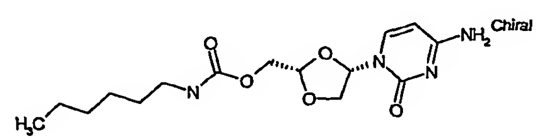
No.	Name	Structure
94	[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 2-isopropyl-5-methyl-cyclohexyl ester	
95	Carbonic acid 4-(4-amino-2-oxo-2#H!-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester 2-isopropyl-5-methyl-cyclohexyl ester	
96	2-METHYL-HEXANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
97	4-AMINO-1-[2-(1-BUTOXY-ETHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
98	(2S,4S) 4-AMINO-1-(2-BENZYLOXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	

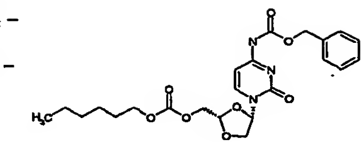
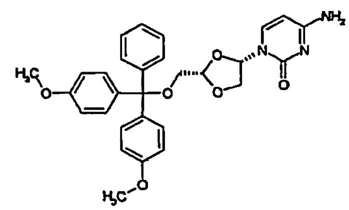
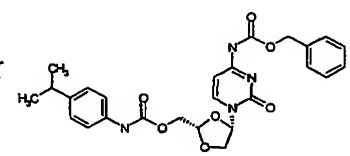
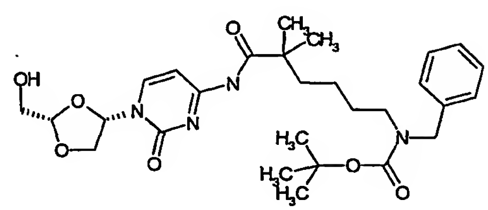
No.	Name	Structure
99	2-ETHYL-HEXANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
100	2,4,6-Triisopropyl-benzoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester	
101	ADAMANTANE-1-CARBOXYLIC ACID 4-(4-BENZYLOXYCARBONYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
102	ADAMANTANE-1-CARBOXYLIC ACID 4-{4-[(ADAMANTANE-1-CARBONYL)-AMINO]-2-OXO-2H-PYRIMIDIN-1-YL}-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
103	CARBONIC ACID 4-[4-(4-CHLORO-PHENOXYCARBONYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-CHLORO-PHENYL ESTER	

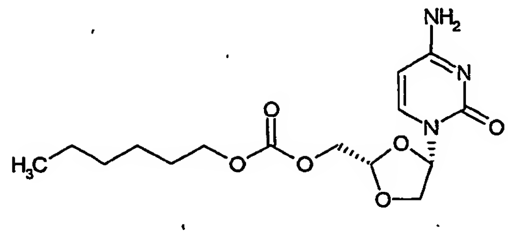
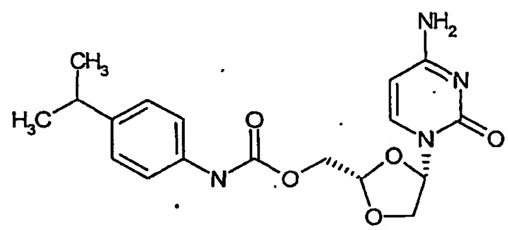
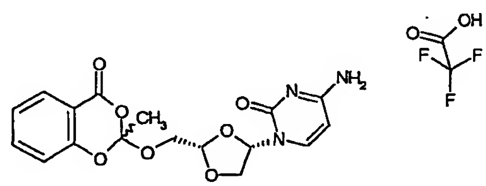
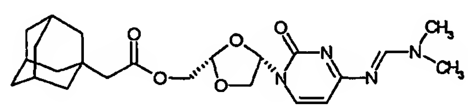
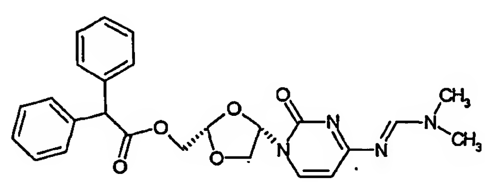
No.	Name	Structure
104	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 4-CHLORO-PHENYL ESTER TRIFLUOROACETATE SALT	
105	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-CHLORO-PHENYL ESTER TRIFLUOROACETATE SALT	
106	(2S,4S)-2-(2''-METHYLPHENYLACETOXY)METHYL-4-(CYTOSIN-1'-YL)-1,3-DIOXOLANE HYDROCHLORIDE	
107	2,2-DIMETHYLHEXANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-1,3-DIOXOLAN-2-YLMETHYL ESTER HYDROCHLORIDE	
108	1-BENZYL-3-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-UREA	

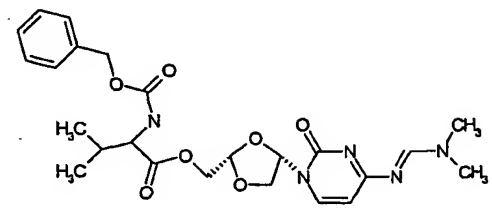
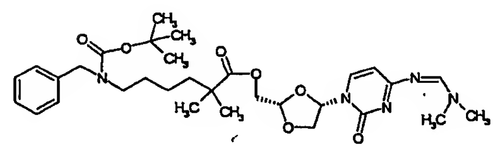
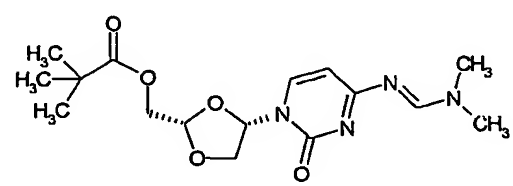
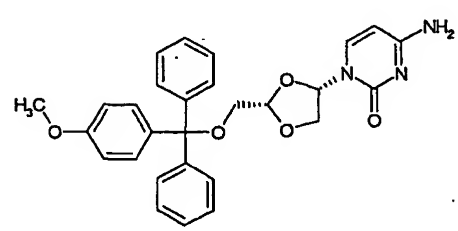
No.	Name	Structure
109	BENZYL-CARBAMIC ACID 4-[4-(3-BENZYL-UREIDO)-2-OXO-2#H!-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
110	ADAMANTANE-1-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
111	5-(BENZYL-TERT-BUTOXYCARBONYL-AMINO)-PENTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
112	CARBONIC ACID 4(S)-(4'-AMINO-2'-OXO-2H-PYRIMIDIN-1'-YL)-[1,3]DIOXOLAN-2(S)-YLMETHYL ESTER 4-(5",6"-DIMETHOXY-1"-OXO-INDAN-2"-YLIDENEMETHYL)-2,6-DIMETHYL-PHENYL ESTER	

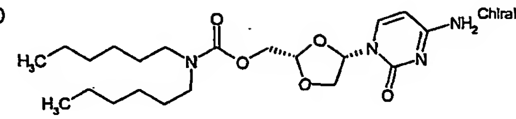
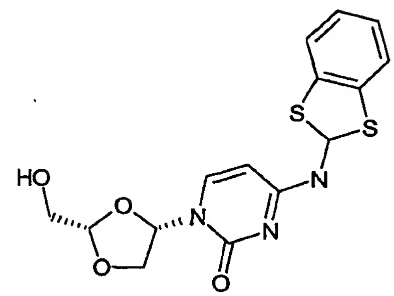
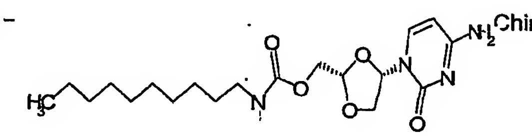
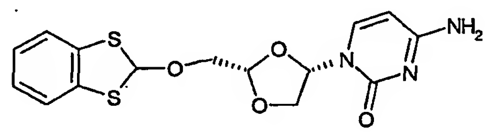
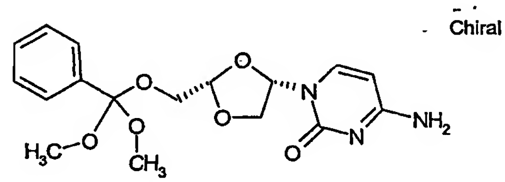
No.	Name	Structure
113	4-AMINO-1-[2-(1-METHOXY-CYCLOHEXYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
114	5-(BENZYL-TERT-BUTOXYCARBONYL-AMINO)-PENTANOIC ACID 4-{4-[5-(BENZYL-TERT-BUTOXYCARBONYL-AMINO)-PENTANOYLAMINO]-2-OXO-2H!PYRIMIDIN-1-YL}-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
115	BENZYL-{4-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYL]-BUTYL}-CARBAMIC ACID TERT!-BUTYL ESTER	
116	CARBONIC ACID 4-(4-BENZYLOXYCARBONYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-METHOXY-PHENYL ESTER	

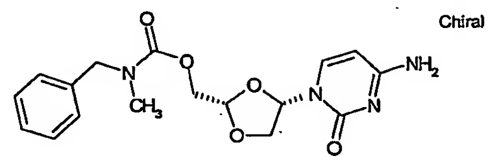
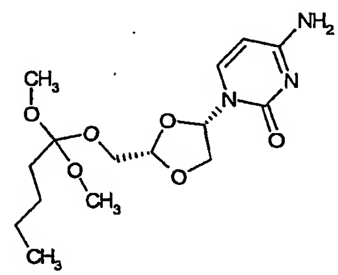
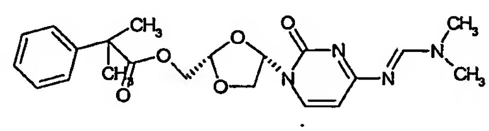
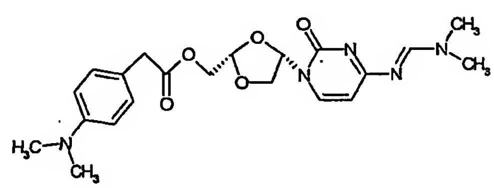
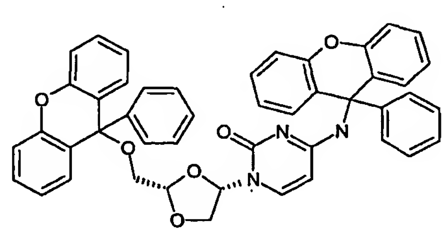
No.	Name	Structure
117	4-AMINO-1-{2-[1-(1,1-DIMETHYL-PROPOXY)-ETHOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-1H-PYRIMIDIN-2-ONE	
118	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-METHOXY-PHENYL ESTER	
119	HEXYL-CARBAMIC ACID 4-[4-(3-HEXYL-UREIDO)-2-OXO-2#H!-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
120	1-HEXYL-3-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-UREA	
121	HEXYL-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	

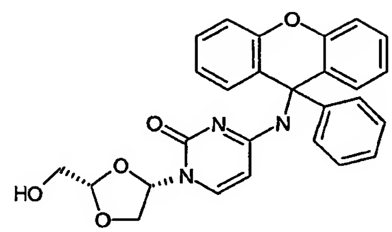
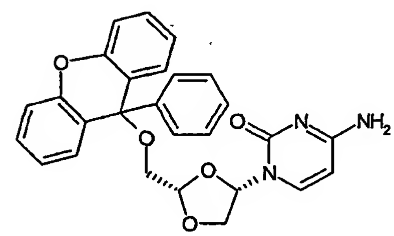
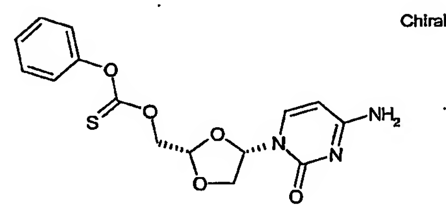
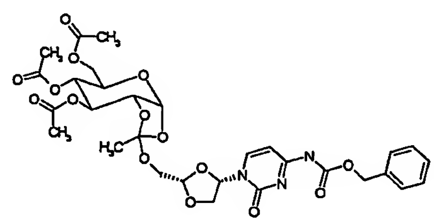
No.	Name	Structure
122	CARBONIC ACID 4-(4-BENZYLOXYCARBONYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER HEXYL ESTER	
123	4-AMINO-1-{2-[BIS-(4-METHOXY-PHENYL)-PHENYL-METHOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-1H-PYRIMIDIN-2-ONE	
124	{1-[2-(4-ISOPROPYL-PHENYLCARBAMOYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL}-CARBAMIC ACID BENZYL ESTER	
125	Benzyl-{5-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-ylcarbamoyl]-5-methyl-hexyl}-carbamic acid tert-butyl ester	

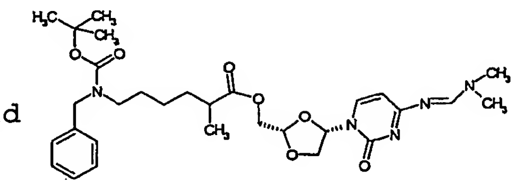
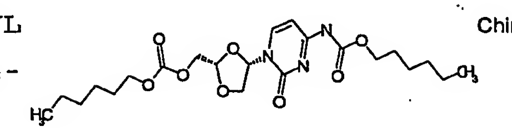
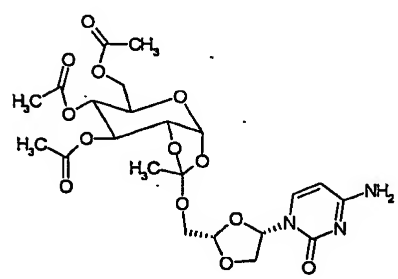
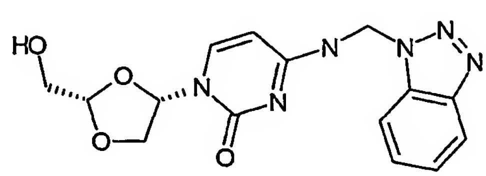
No.	Name	Structure
126	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER HEXYL ESTER	
127	(4-ISOPROPYL-PHENYL)-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
128	4-AMINO-1-[5-(2-METHYL-4-OXO-4#H!-BENZO[1,3]DIOXIN-2-YLOXYMETHYL)-TETRAHYDRO-FURAN-2-YL]-1#H!-PYRIMIDIN-2-ONE; COMPOUND WITH TRIFLUORO-ACETIC ACID	
129	(2S,4S)-2-(1''-ADMANTANEACETOXY)METHYL-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
130	(2S,4S)-2-(2''-DIPHENYLACETOXYMETHYL)-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	

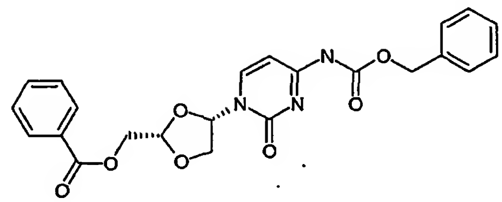
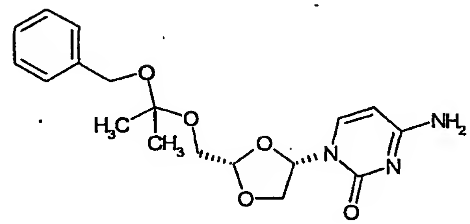
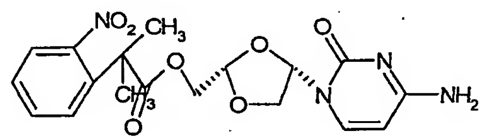
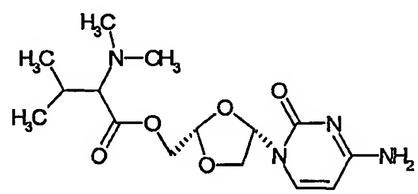
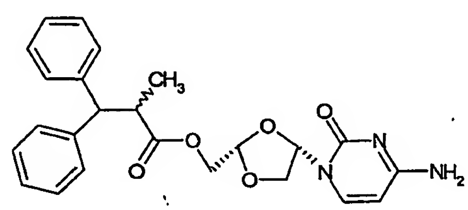
No.	Name	Structure
131	(2S,4S)-2-(BENZYLOXYCARBONYL-L-VALINOXYMETHYL)-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
132	6-(Benzyl-tert-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2H-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester	
133	2,2-Dimethyl-propionic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2H-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester	
134	4-AMINO-1-{2-[(4-METHOXY-PHENYL)-DIPHENYL-METHOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-1H-PYRIMIDIN-2-ONE	

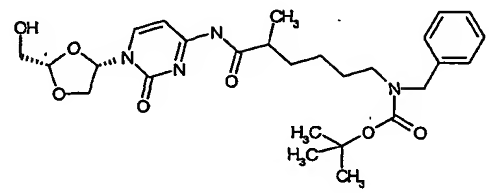
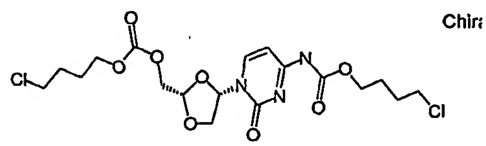
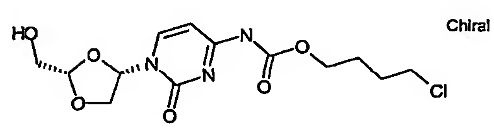
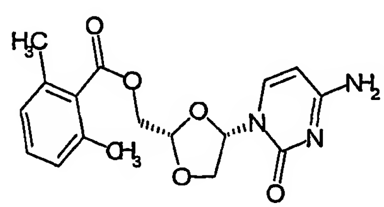
No.	Name	Structure
135	DIHEXYLCARBAMIC ACID 4(S)-(4'-AMINO-2'-OXO-2H-PYRIMIDIN-1'-YL)-[1,3]DIOXOLAN-2(S)-YLMETHYL ESTER	
136	4-(BENZO[1,3]DITHIOL-2-YLAMINO)-1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H!PYRIMIDIN-2-ONE	
137	DECYL-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
138	4-AMINO-1-[2-(BENZO[1,3]DITHIOL-2-YLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
139	4-AMINO-1-[2-(DIMETHOXY-PHENYL-METHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	

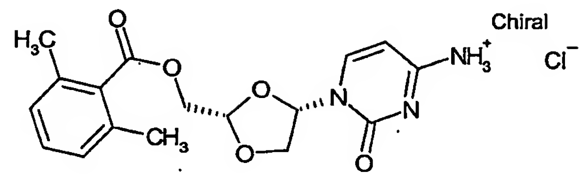
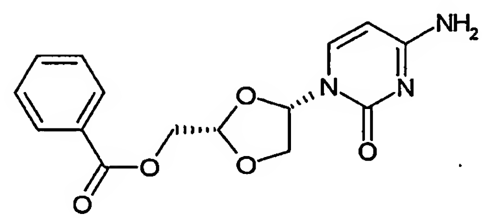
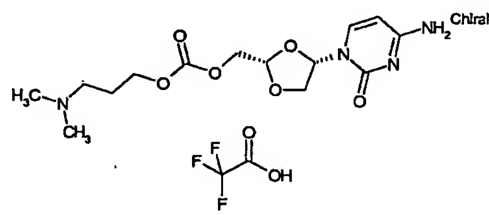
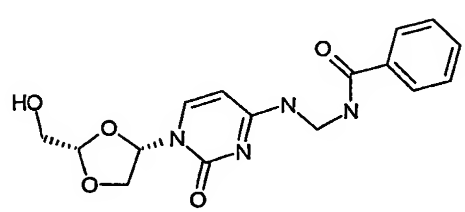
No.	Name	Structure
140.	BENZYL-METHYL-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
141	4-AMINO-1-[2-(1,1-DIMETHOXY-PENTYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
142	(2S,4S)-2-(2''-DIMETHYLPHENYLACETOXY)METHYL-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1,-YL)-1,3-DIOXOLANE	
143	(2S,4S)-2-(4''-N,N-DIMETHYLAMINOPHENYLACETOXY)METHYL-4-(4'-N,N-DIMETHYLAMINOMETHYLENE-CYTOSIN-1'-YL)-1,3-DIOXOLANE	
144	4-(9-PHENYL-9#H!-XANTHEN-9-YLAMINO)-1-[2-(9-PHENYL-9#H!-XANTHEN-9-YLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1#H!-PYRIMIDIN-2-ONE	

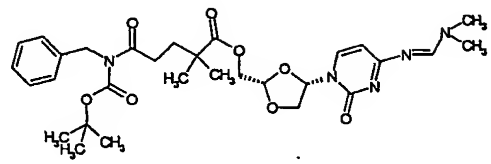
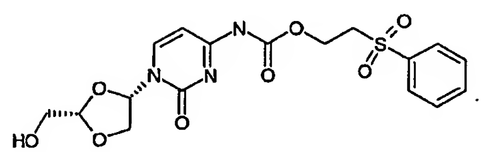
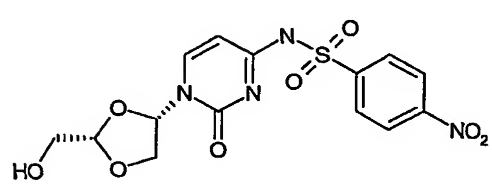
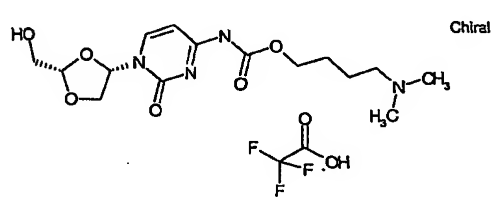
No.	Name	Structure
145	1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-4-(9-PHENYL-9#H!-XANTHEN-9-YLAMINO)-1#H!-PYRIMIDIN-2-ONE	
146	4-AMINO-1-[2-(9-PHENYL-9#H!-XANTHEN-9-YLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1#H!-PYRIMIDIN-2-ONE	
147	THIOCARBONIC ACID O-[4(S)-(4'-AMINO-2'-OXO-2H-PYRIMIDIN-1'-YL)-[1,3]DIOXOLAN-2(S)-YLMETHYL] ESTER O-PHENYL ESTER	
148	Acetic acid 6-acetoxy-5-acetoxymethyl-2-[4-(4-benzyloxycarbonylamino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethoxy]-2-methyl-tetrahydro-[1,3]dioxolo[4,5-b]pyran-7-yl ester	

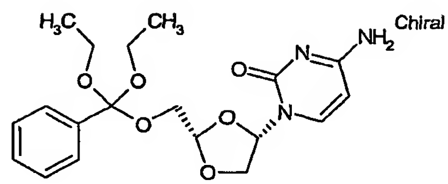
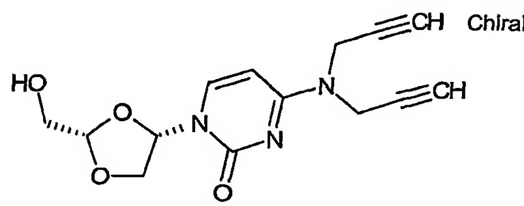
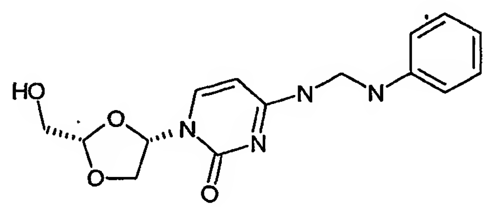
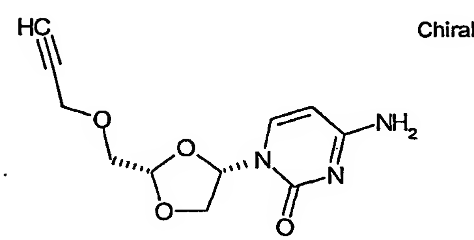
No.	Name	Structure
149	6-(Benzyl-tert-butoxycarbonyl-amino)-2-methyl-hexanoic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2H-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester	
150	CARBONIC ACID HEXYL ESTER 4-(4-HEXYLOXYCARBONYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
151	Acetic acid 6-acetoxy-5-acetoxymethyl-2-[4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethoxy]-2-methyl-tetrahydro-[1,3]dioxolo[4,5-b]pyran-7-yl ester	
152	4-[(BENZOTRIAZOL-1-YLMETHYL)-AMINO]-1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	

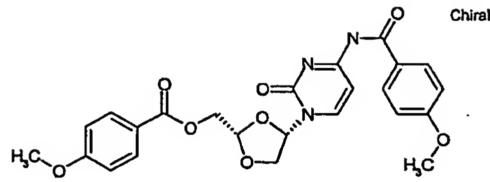
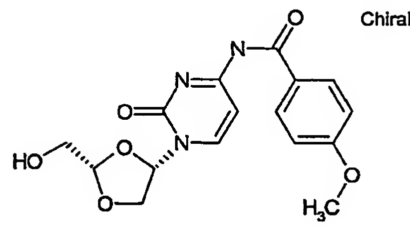
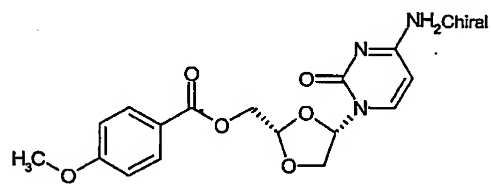
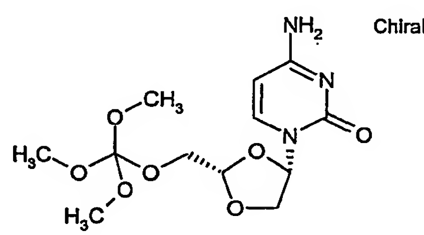
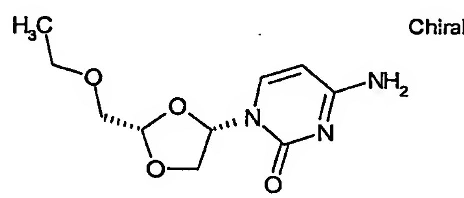
No.	Name	Structure
153	BENZOIC ACID 4-(4-BENZYLOXYCARBONYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
154	4-AMINO-1-[2-(1-BENZYLOXY-1-METHYL-ETHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
155	(2S,4S)-2-[2''-(2'''-NITROPHENYL)-2"-METHYLPROPIONYLOXYMETHYL]-4-CYTOSIN-1'-YL-1,3-DIOXOLANE	
156	(2S,4S)-2-(N,N-DIMETHYL-L-VALINYLOXYMETHYL)-4-CYTOSIN-1'-YL-1,3-DIOXOLANE	
157	(2S,4S)-(3"-DIPHENYL-2"-METHYLPROPIOXYMETHYL)-4-CYTOSIN-1'-YL-1,3-DIOXOLANE	

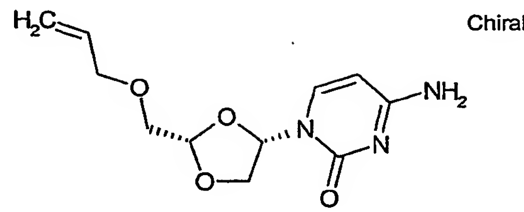
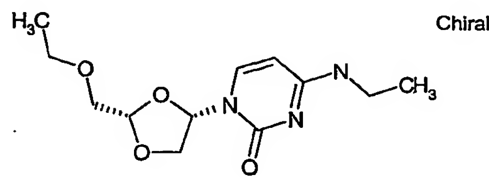
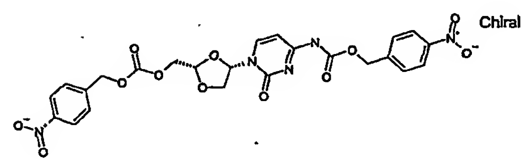
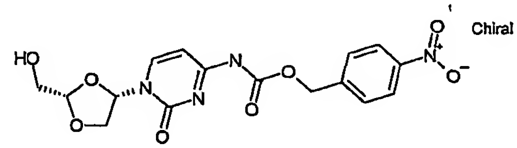
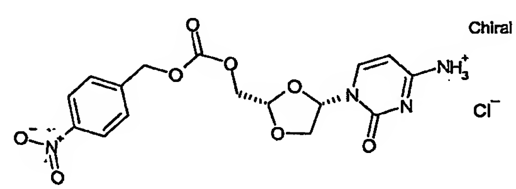
No.	Name	Structure
158	Benzyl-{5-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-ylcarbamoyl]-hexyl}-carbamic acid tert-butyl ester	
159	CARBONIC ACID 4-[4-(4-CHLORO-BUTOXYCARBONYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-CHLORO-BUTYL ESTER	
160	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 4-CHLORO-BUTYL ESTER	
161	2,6-Dimethyl-benzoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester	

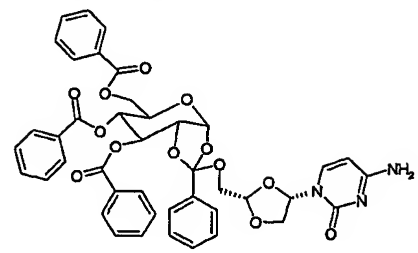
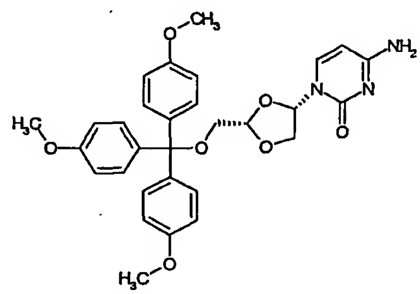
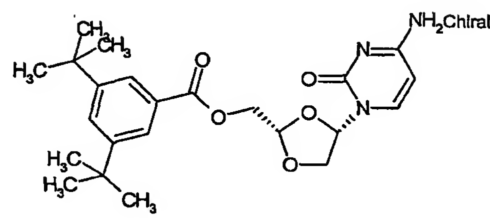
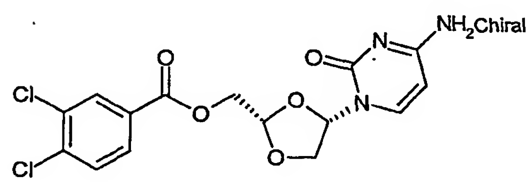
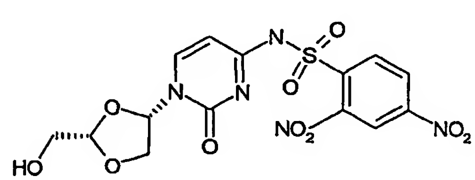
No.	Name	Structure
162	1-[2-(2,6-DIMETHYL-BENZOYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL-AMMONIUM; CHLORIDE	
163	BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
164	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER 3-DIMETHYLAMINO-PROPYL ESTER TRIFLUORO-ACETIC ACID SALT	
165	N-{[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLAMINO]-METHYL}-BENZAMIDE	

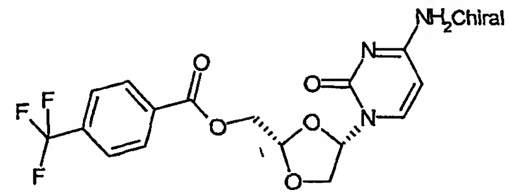
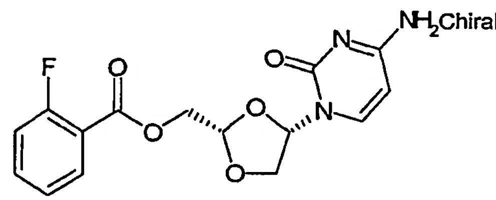
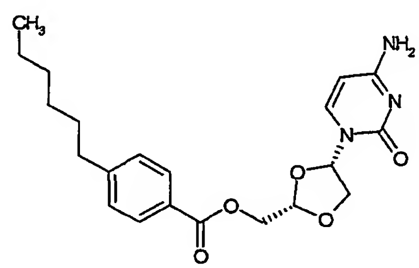
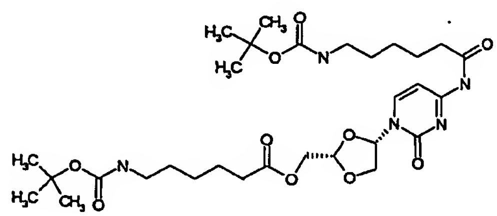
No.	Name	Structure
166	5-(Benzyl-tert-butoxycarbonyl-amino)-2,2-dimethyl-5-oxo-pentanoic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2H-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester	
167	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 2-BENZENESULFONYL-ETHYL ESTER	
168	N-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-4-NITRO-BENZENESULFONAMIDE	
169	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 4-DIMETHYLAMINO-BUTYL ESTER TRIFLUOROACETIC ACID SALT	

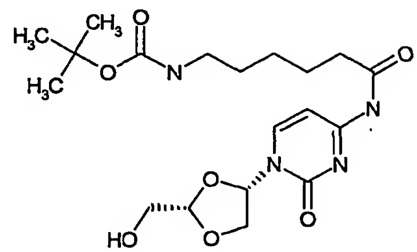
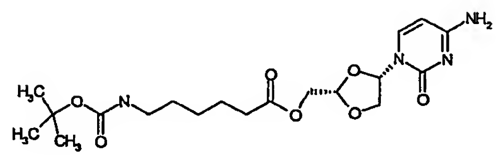
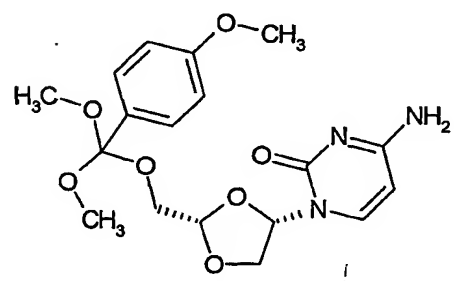
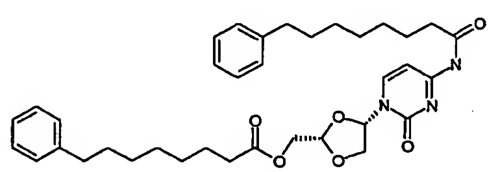
No.	Name	Structure
170	4-AMINO-1-[2-(DIETHOXY-PHENYL-METHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1H-PYRIMIDIN-2-ONE	
171	(S,S) 4-(DI-PROP-2'-YNYL-AMINO)-1-(2"-HYDROXYMETHYL-[1,3]DIOXOLAN-4"-YL)-1H-PYRIMIDIN-2-ONE	
172	1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-4-(PHENYLAMINOMETHYL-AMINO)-1H-PYRIMIDIN-2-ONE	
173	(S,S)-4-AMINO-1-(2'-PROP-2'-YNYLOXYMETHYL-[1,3]DIOXOLAN-4'-YL)-1H-PYRIMIDIN-2-ONE	

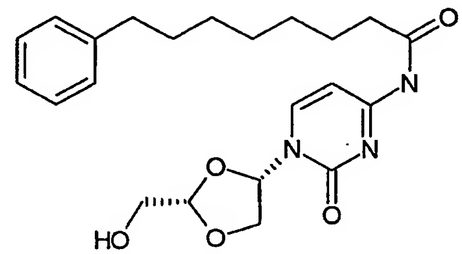
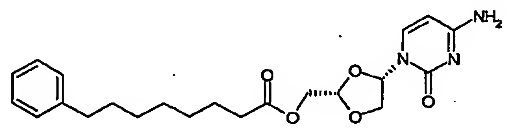
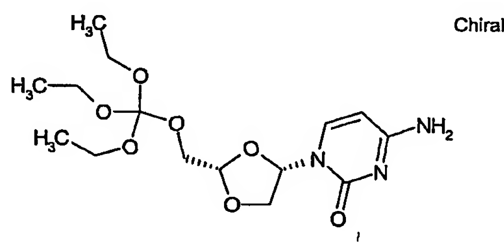
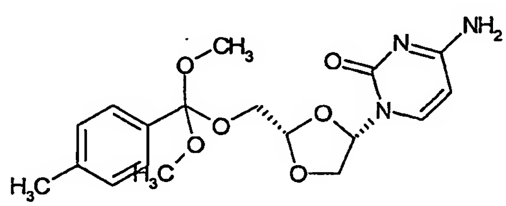
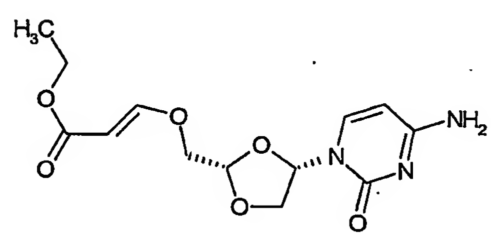
No.	Name	Structure
174	4-METHOXY-BENZOIC ACID 4-[4-(4-METHOXY-BENZOYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
175	N-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-4-METHOXY-BENZAMIDE	
176	4-METHOXY-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
177	4-AMINO-1-(2-TRIMETHOXYMETHOXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	
178	(S,S)-4-AMINO-1-(2'-ETHOXYMETHYL-[1,3]DIOXOLAN-4'-YL)-1H-PYRIMIDIN-2-ONE	

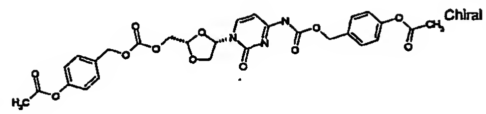
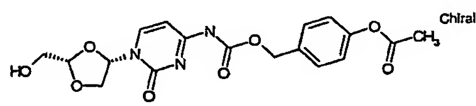
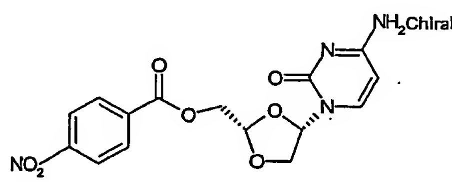
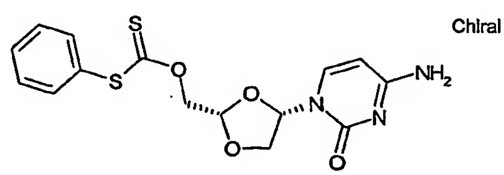
No.	Name	Structure
179	(S,S)-1-(2'-ALLYLOXYMETHYL-[1,3]DIOXOLAN-4'-YL)-4-AMINO-1H-PYRIMIDIN-2-ONE	
180	(S,S)-1-(2'-ETHOXYMETHYL-[1,3]DIOXOLAN-4'-YL)-4-ETHYLAMINO-1H-PYRIMIDIN-2-ONE	
181	CARBONIC ACID 4-NITRO-BENZYL ESTER 4-[4-(4-NITRO-BENZYLOXYCARBONYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
182	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 4-NITRO-BENZYL ESTER	
183	CARBONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER 4-NITRO-BENZYL ESTER HYDROCHLORIDE SALT	

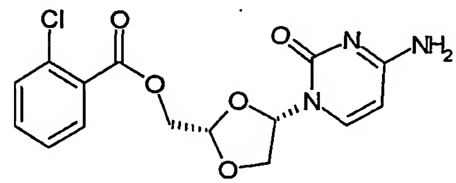
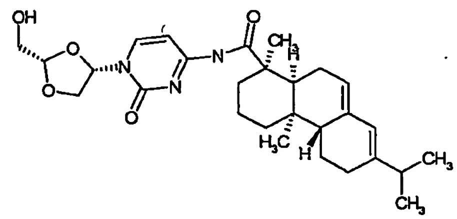
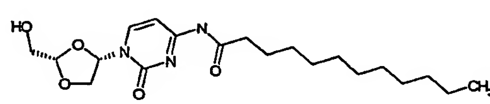
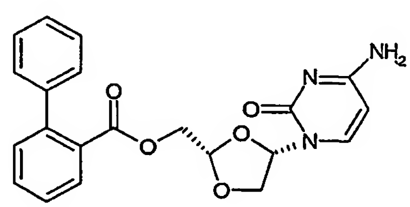
No.	Name	Structure
184	3,4,6-TRI-O-BENZOYL-1,2-O-(1-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYLOXY)-BENZYL)-□˜D-GLUCOPYRANOSe	
185	4-AMINO-1-{2-[TRIS-(4-METHOXY-PHENYL)-METHOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-1H-PYRIMIDIN-2-ONE	
186	3,5-DI-TERT-BUTYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
187	3,4-DICHLORO-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
188	N-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-2,4-DINITRO-BENZENESULFONAMIDE	

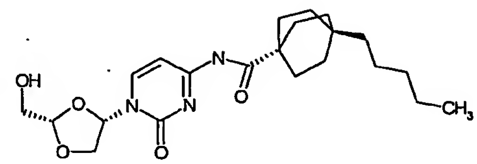
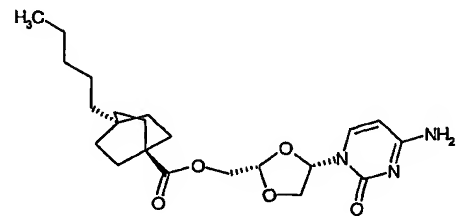
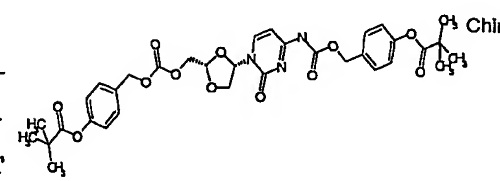
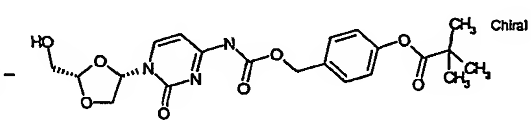
No.	Name	Structure
189	4-TRIFLUOROMETHYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
190	2-FLUORO-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
191	4-HEXYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
192	6-TERT!-BUTOXYCARBONYLAMINO-HEXANOIC ACID 4-[4-(6-TERT-BUTOXYCARBONYLAMINO-HEXANOYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YL METHYL ESTER	

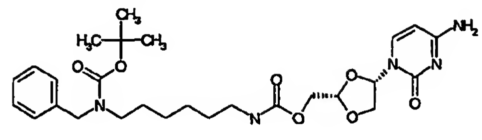
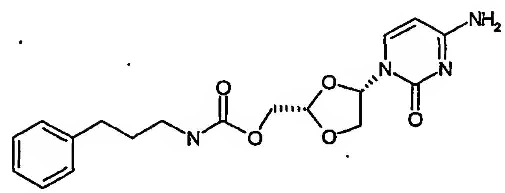
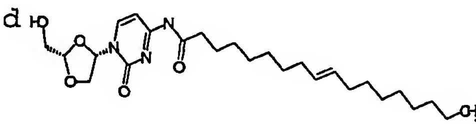
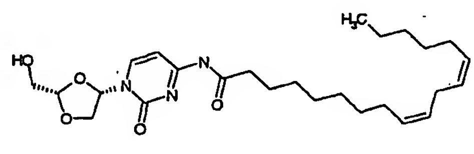
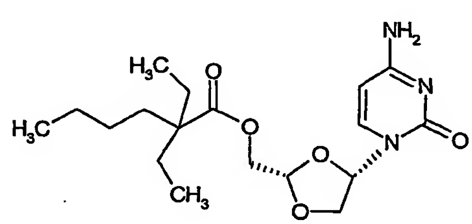
No.	Name	Structure
193	{5-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYL]-PENTYL}-CARBAMIC ACID TERT-BUTYL ESTER	
194	6-TERT!-BUTOXYCARBONYLAMINO-HEXANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	
195	4-AMINO-1-{2-[DIMETHOXY-(4-METHOXY-PHENYL)-METHOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-1#H!-PYRIMIDIN-2-ONE	
196	8-PHENYL-OCTANOIC ACID 4-[2-OXO-4-(8-PHENYL-OCTANOYLAMINO)-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YL METHYL ESTER	

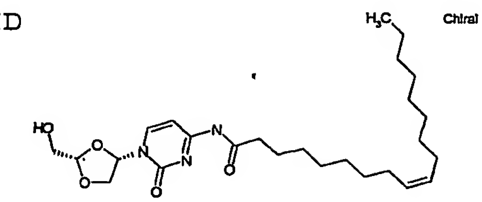
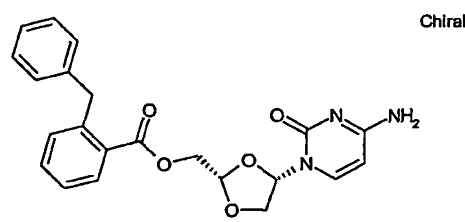
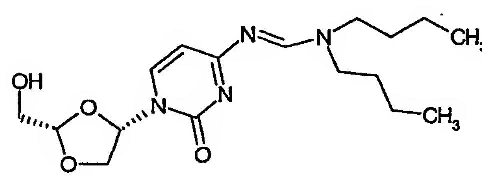
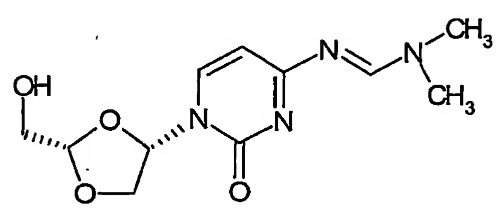
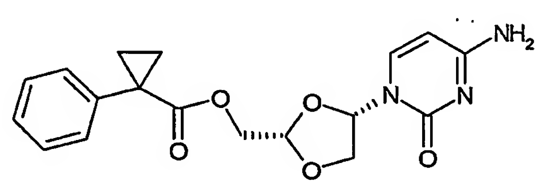
No.	Name	Structure
197	8-PHENYL-OCTANOIC. ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
198	8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
199	4-Amino-1-(2-triethoxymethoxymethyl-[1,3]dioxolan-4-yl)-1H-pyrimidin-2-one	
200	4-AMINO-1-[2-(DIMETHOXY-#P!-TOLYL-METHOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1#H!-PYRIMIDIN-2-ONE	
201	3-[4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHOXY]-ACRYLIC ACID ETHYL ESTER	

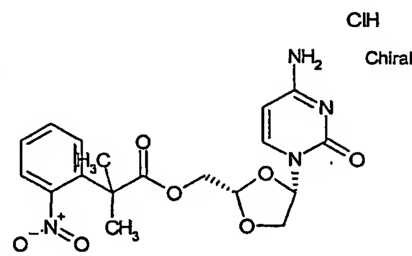
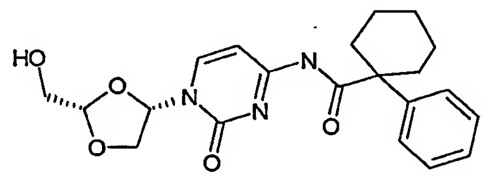
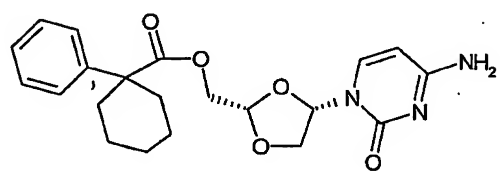
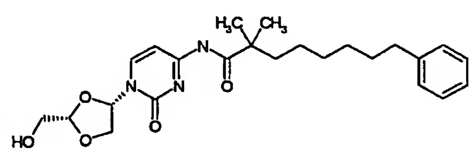
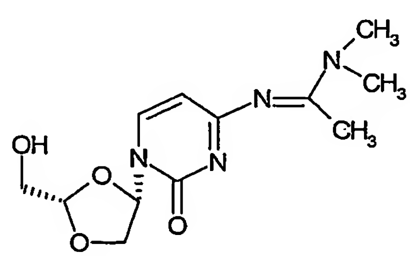
No.	Name	Structure
202	ACETIC ACID 4-{1-[2-(4-ACETOXY-BENZYLOXYCARBONYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL CARBAMOYLOXYMETHYL}-PHENYL ESTER	
203	ACETIC ACID 4-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYLOXYMETHYL]-PHENYL ESTER	
204	4-NITRO-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
205	DITHIOCARBONIC ACID O-[4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL] ESTER S-PHENYL ESTER	

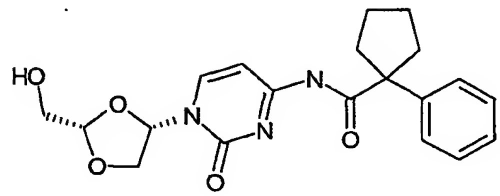
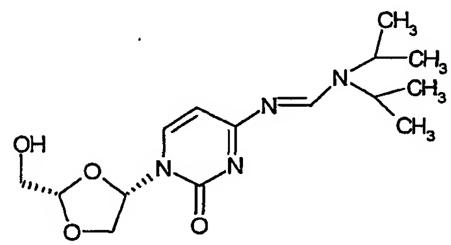
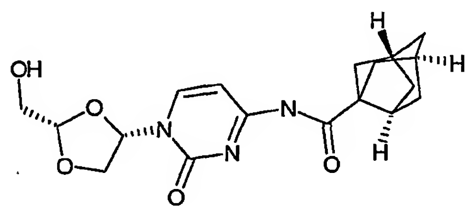
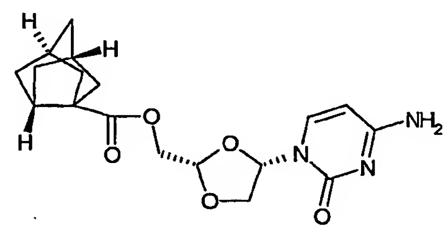
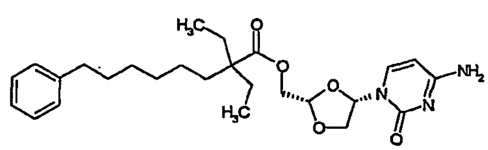
No.	Name	Structure
206	2-CHLORO-BENZOIC ACID 4-(4-AMINO-2-OXO-2#H!-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
207	7-ISOPROPYL-2,4A-DIMETHYL-1,2,3,4,4A,4B,5,6,10,10A-DECAHYDRO-PHENANTHRENE-2-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
208	DODECANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	 Chiral
209	BIPHENYL-2-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2#H!-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	

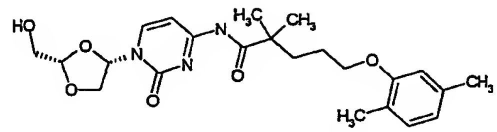
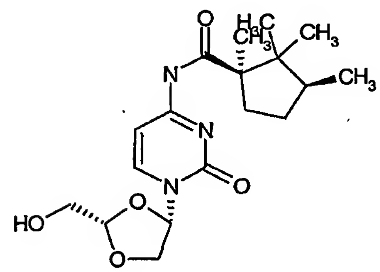
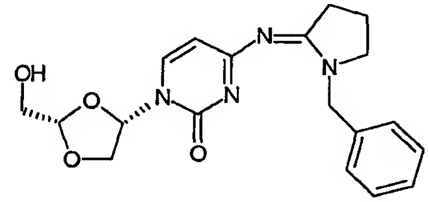
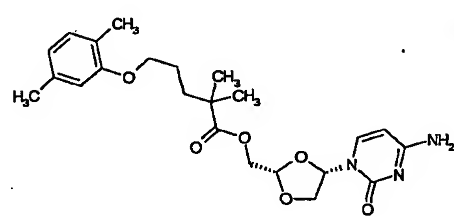
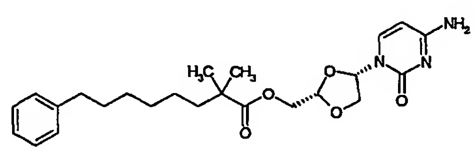
No.	Name	Structure
210	4-PENTYL-BICYCLO[2.2.2]OCTANE-1-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
211	4-PENTYL-BICYCLO[2.2.2]OCTANE-1-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
212	2,2-DIMETHYL-PROPIONIC ACID 4-(1-{2-[4-(2,2-DIMETHYL-PROPIONYLOXY)-BENZYLOXYCARBONYLOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYLOXYMETHYL)-PHENYL ESTER	
213	2,2-DIMETHYL-PROPIONIC ACID 4-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYLOXYMETHYL]-PHENYL ESTER	

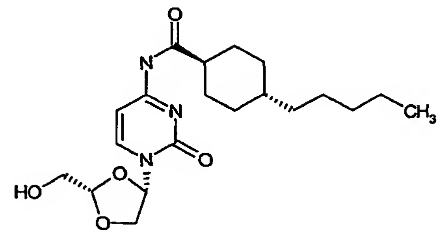
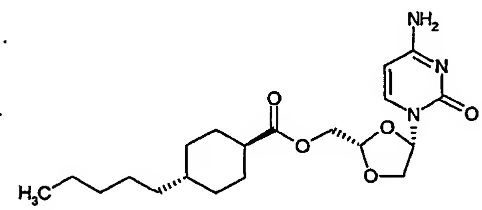
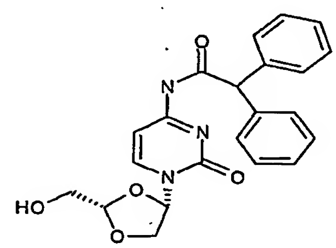
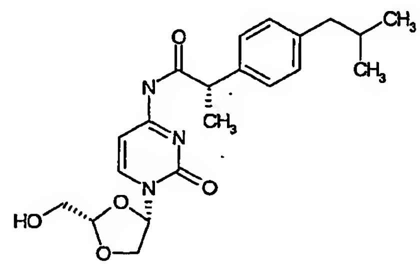
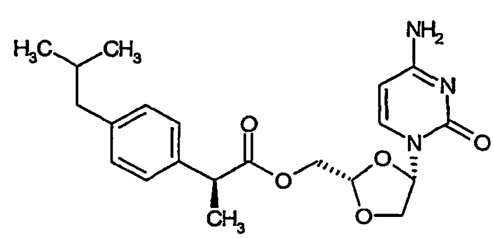
No.	Name	Structure
214	{6-[4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHOXYCARBONYLAMINO]-HEXYL}-BENZYL-CARBAMIC ACID TERT-BUTYL ESTER	
215	(3-PHENYL-PROPYL)-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
216	Octadec-9-enoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide	
217	OCTADECA-9,12-DIENOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
218	2,2-DIETHYL-HEXANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	

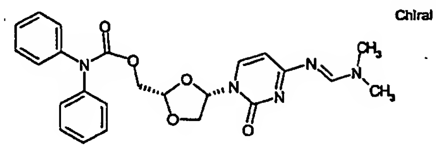
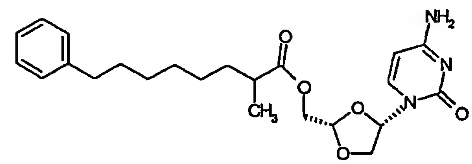
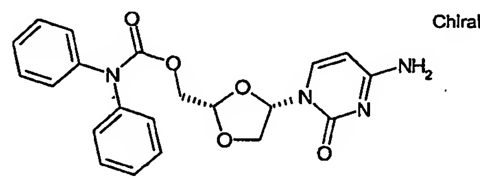
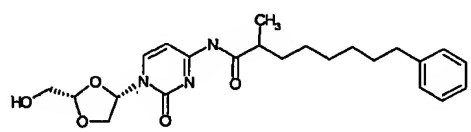
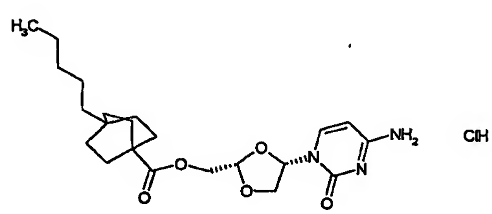
No.	Name	Structure
219	OCTADEC-9-ENOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
220	BIPHENYL-2-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
221	N,N-Dibutyl-N'-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-formamidine	
222	N'-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-N,N-DIMETHYL-FORMAMIDINE	
223	1-PHENYL-CYCLOPROPANECARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	

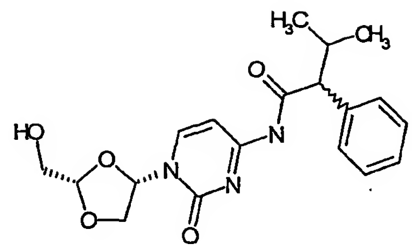
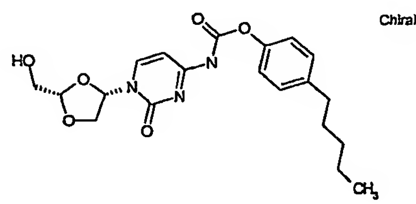
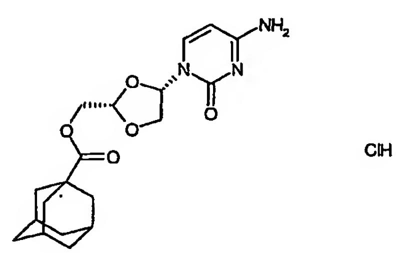
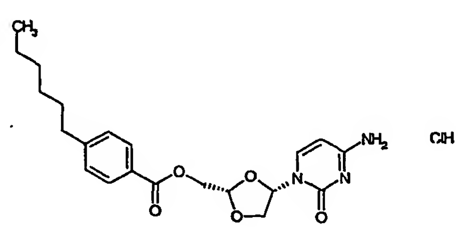
No.	Name	Structure
224	2-METHYL-2-(2-NITRO-PHENYL)-PROPIONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER HYDROCHLORIDE SALT	
225	1-PHENYL-CYCLOHEXANECARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
226	1-PHENYL-CYCLOHEXANECARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
227	2,2-DIMETHYL-8-PHENYL-OCTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
228	N'-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-N,N-DIMETHYL-ACETAMIDINE	

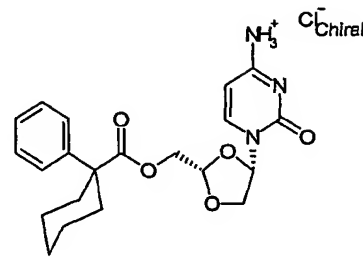
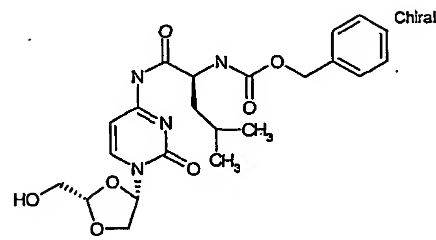
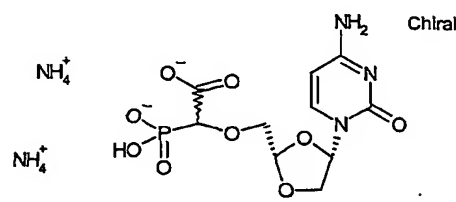
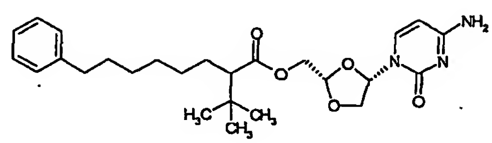
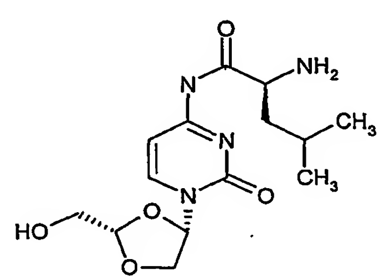
No.	Name	Structure
229	1-PHENYL-CYCLOPENTANECARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
230	N'-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-N,N-DIISOPROPYL-FORMAMIDINE	
231	HEXAHYDRO-2,5-METHANO-PENTALENE-3A-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
232	HEXAHYDRO-2,5-METHANO-PENTALENE-3A-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
233	2,2-DIETHYL-8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	

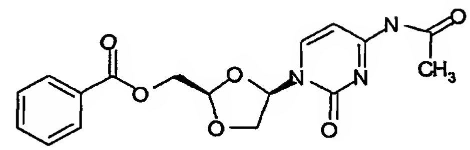
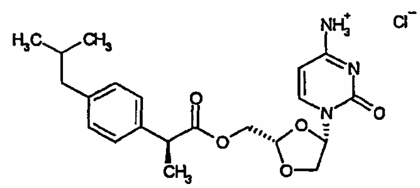
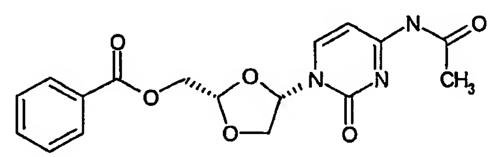
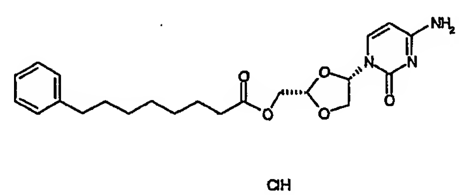
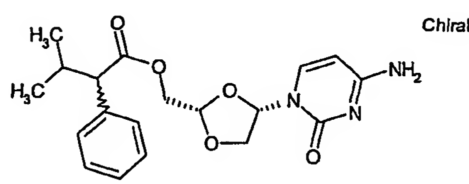
No.	Name	Structure
234	5-(2,5-DIMETHYL-PHENOXY)-2,2-DIMETHYL-PENTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
235	1,2,2,3-TETRAMETHYL-CYCLOPENTANECARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
236	4-(1-BENZYL-PYRROLIDIN-2-YLIDENEAMINO)-1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-1H-PYRIMIDIN-2-ONE	
237	4-AMINO-1-{2-[4-(2,5-DIMETHYL-PHENOXY)-1,1-DIMETHYL-BUTOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-1H-PYRIMIDIN-2-ONE	 Chiral
238	2,2-DIMETHYL-8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	

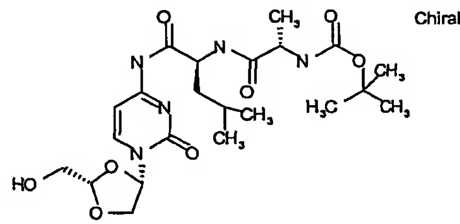
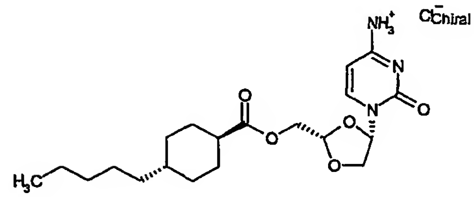
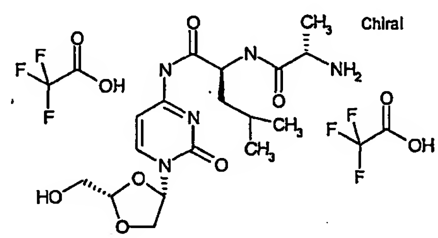
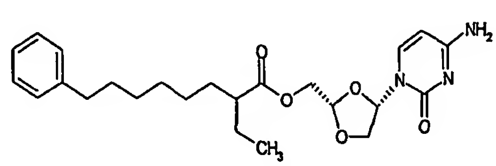
No.	Name	Structure
239	4-PENTYL-CYCLOHEXANECARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	
240	4-PENTYL-CYCLOHEXANECARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
241	N-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-2,2-DIPHENYL-ACETAMIDE	
242	N-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-2-(4-ISOBUTYL-PHENYL)-PROPIONAMIDE	
243	2-(4-ISOBUTYL-PHENYL)-PROPIONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	

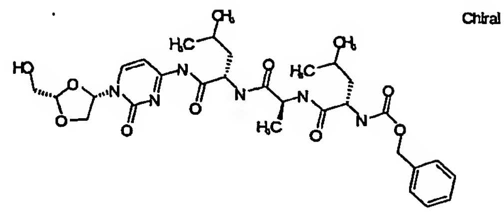
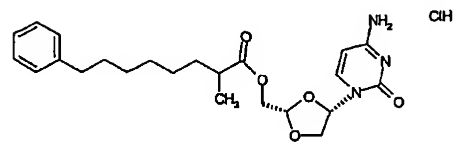
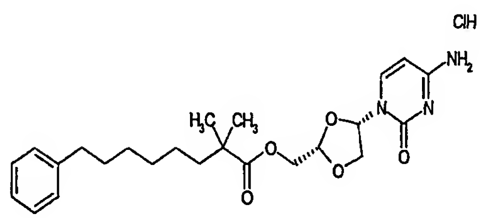
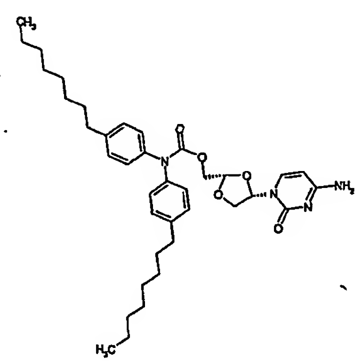
No.	Name	Structure
244	DIPHENYL-CARBAMIC ACID 4-[4-(DIMETHYLAMINO-METHYLENEAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YL METHYL ESTER	
245	2-METHYL-8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
246	DIPHENYL-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
247	2-Methyl-8-phenyl-octanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide	
248	4-PENTYL-BICYCLO[2.2.2]OCTANE-1-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER;HYDROCHLORIDE	

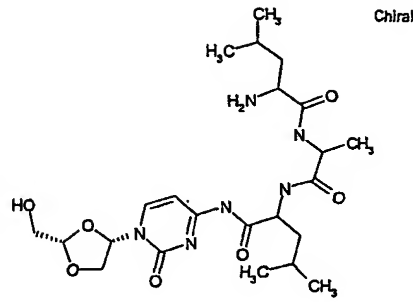
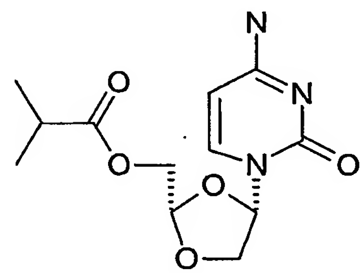
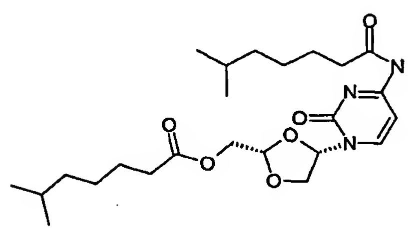
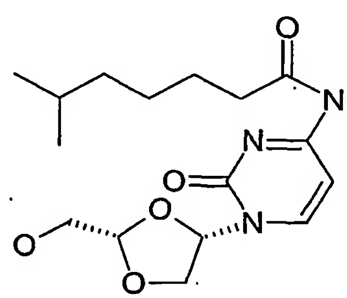
No.	Name	Structure
	SALT	
249	#N!-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-3-METHYL-2-PHENYL-BUTYRAMIDE	
250	[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-CARBAMIC ACID 4-PENTYL-PHENYL ESTER	
251	Adamantane-1-carboxylic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester	
252	4-HEXYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER; HYDROCHLORIDE SALT	

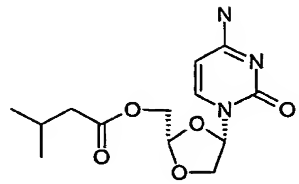
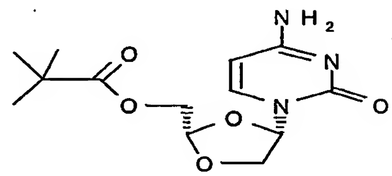
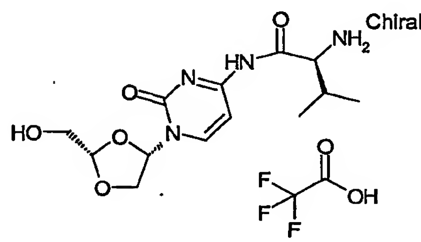
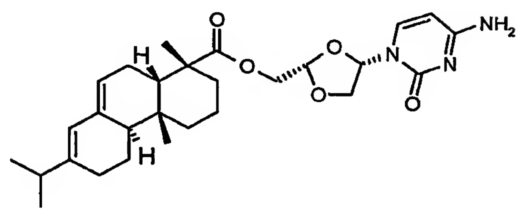
No.	Name	Structure
253	2-OXO-1-[2-(1-PHENYL-CYCLOHEXANECARBONYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1,2-DIHYDRO-PYRIMIDIN-4-YL-AMMONIUM; CHLORIDE	
254	{1-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL CARBAMOYL]-3-METHYL-BUTYL}-CARBAMIC ACID BENZYL ESTER	
255	[4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHOXY]-PHOSPHONO-ACETATE BIS-AMMONIUM SALT	
256	2-tert-Butyl-8-phenyl-octanoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester	
257	2-AMINO-4-METHYL-PENTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	

No.	Name	Structure
258	BENZOIC ACID 4-(4-ACETYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
259	BENZOIC ACID 4-(4-ACETYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
260	1-{2-[2-(4-ISOBUTYL-PHENYL)-PROPIONYLOXYMETHYL]-[1,3]DIOXOLAN-4-YL}-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL-AMMONIUM; CHLORIDE	
261	8-Phenyl-octanoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-yl methyl ester hydrochloride	
262	3-METHYL-2-PHENYL-BUTYRIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	

No.	Name	Structure
263	(1-{1-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYL]-3-METHYL-BUTYLCARBAMOYL}-ETHYL)-CARBAMIC ACID TERT-BUTYL ESTER	
264	2-OXO-1-[2-(4-PENTYL-CYCLOHEXANECARBONYLOXYMETHYL)-[1,3]DIOXOLAN-4-YL]-1,2-DIHYDRO-PYRIMIDIN-4-YL-AMMONIUM CHLORIDE	
265	2-(2-AMINO-PROPIONYLAMINO)-4-METHYL-PENTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE, BIS TRIFLUOROACETIC ACID SALT	
266	2-ETHYL-8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	

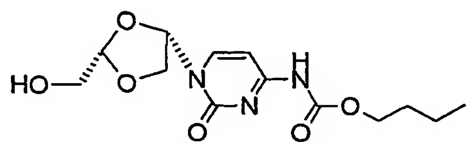
No.	Name	Structure
267	[1-(1-{1-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YLCARBAMOYL]-3-METHYL-BUTYLCARBAMOYL}-ETHYLCARBAMOYL)-3-METHYL-BUTYL]-CARBAMIC ACID BENZYL ESTER	
268	2-METHYL-8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER HYDROCHLORIDE	
269	2,2-DIMETHYL-8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER HYDROCHLORIDE	
270	BIS-(4-OCTYL-PHENYL)-CARBAMIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER	

No.	Name	Structure
272	2-AMINO-4-METHYL-PENTANOIC ACID (1-{1-[1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL CARBAMOYL]-3-METHYL-BUTYLCARBAMOYL}-ETHYL)-AMIDE	
275	ISOBUTYRIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
276	6-METHYL-HEPTANOIC ACID 4-[4-(6-METHYL-HEPTANOYLAMINO)-2-OXO-2H-PYRIMIDIN-1-YL]-[1,3]DIOXOLAN-2-YL METHYL ESTER	
277	6-METHYL-HEPTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE	

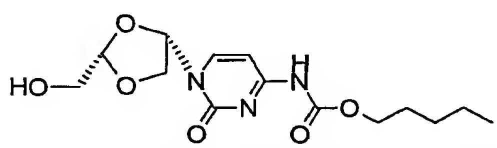
No.	Name	Structure
278	3-METHYL-BUTYRIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
279	2,2-DIMETHYL-PROPIONIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YL METHYL ESTER	
280	2-Amino-N-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-3-methyl-butyramide; trifluoroacetic acid salt	
281	7-ISOPROPYL-2,4A-DIMETHYL-1,2,3,4,4A,4B,5,6,10,10A-DECAHYDRO-PHENANTHRENE-2-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-ESTER	

The following are examples of additional compounds in accordance with the invention:

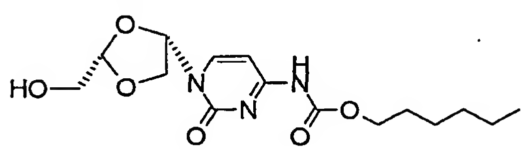
[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid butyl ester



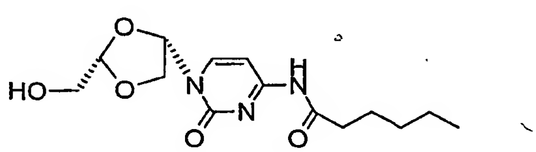
[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid pentyl ester



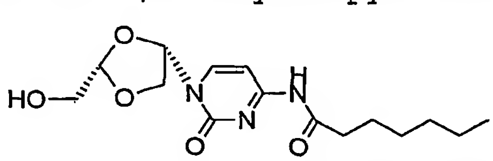
[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid hexyl ester



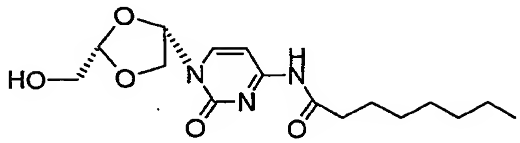
Hexanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



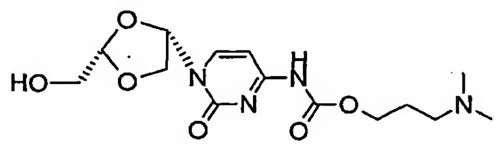
Heptanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



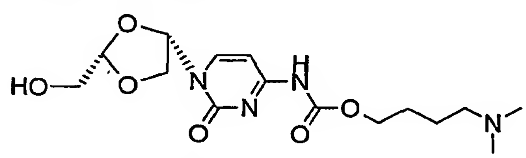
Octanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



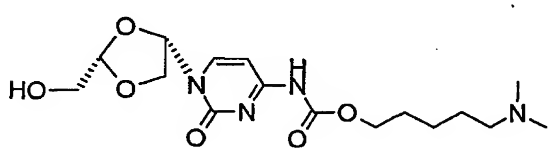
[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 3-dimethylamino-propyl ester



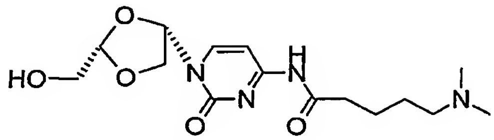
[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 4-dimethylamino-butyl ester



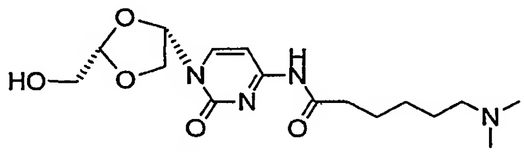
[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 5-dimethylamino-pentyl ester



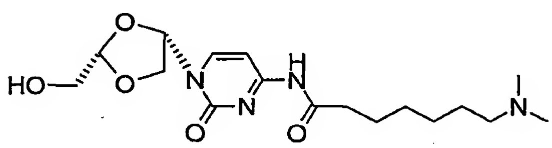
5-Dimethylamino-pentanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



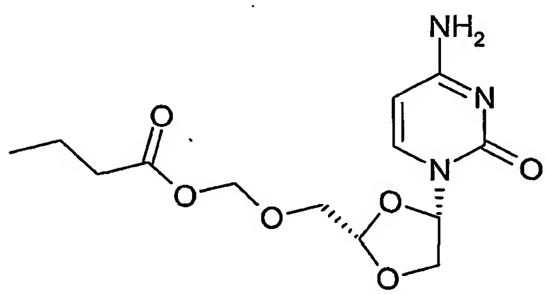
6-Dimethylamino-hexanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



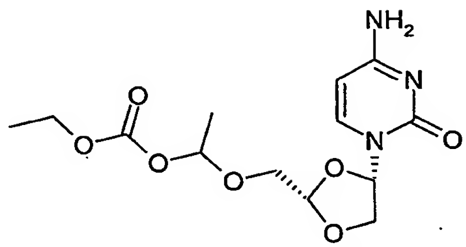
7-Dimethylamino-heptanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



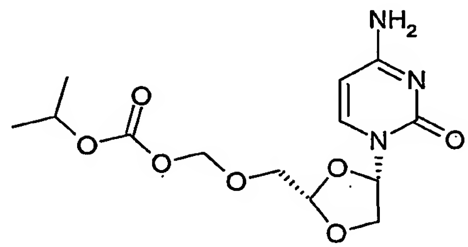
Acetic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethoxymethyl ester



Butyric acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethoxymethyl ester



Carbonic acid 1-[4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethoxy]-ethyl ester ethyl ester



Carbonic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3] dioxolan-2-ylmethoxymethyl ester isopropyl ester

(2S, 4S) N-[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-2-piperidin-4-yl-acetamide trifluoroacetate salt

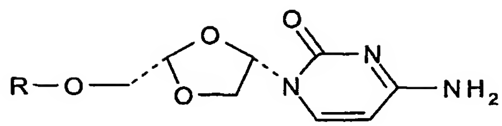
(2S, 4S) Piperidin-4-yl-acetic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester trifluoroacetate salt

(2S, 4S) 2-Amino-3-methyl-butyric acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester trifluoroacetate salt

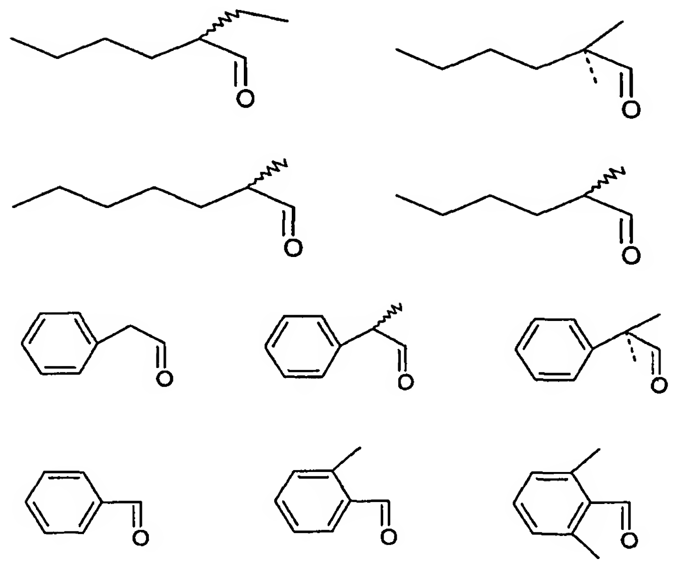
(2S, 4S) 2-Amino-N-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-3-methyl-butyramide trifluoroacetate salt

(2S, 4S) 4-Amino-1-[2-(tetrahydro-pyran-2-yloxymethyl)-[1,3]dioxolan-4-yl]-1H-pyrimidin-2-one

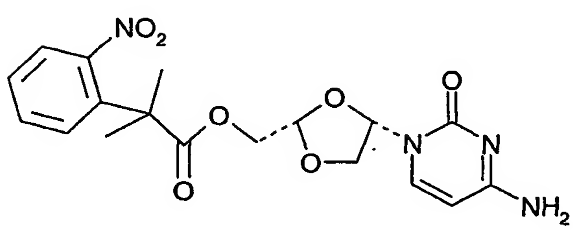
Additional exemplary compounds are illustrated below:

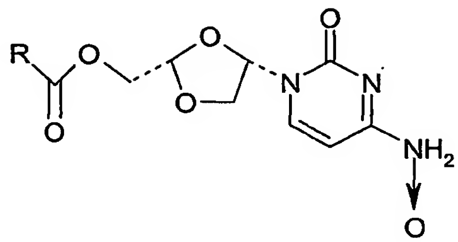


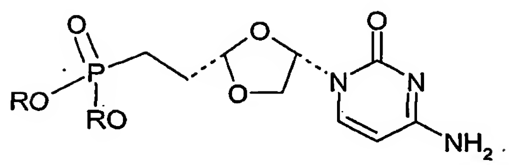
R =

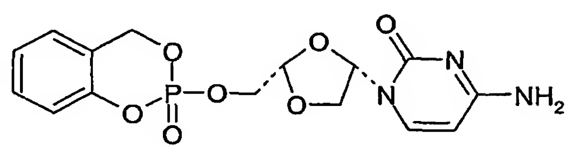


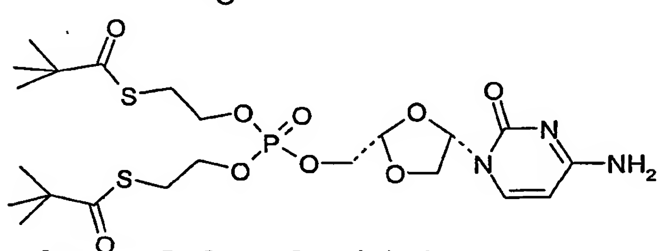
Further examples are:











The compounds of formula (I) have a cis geometrical configuration. Moreover, the compounds of formula (I) exhibit the ''unnatural'' nucleoside configuration, that is they are L-enantiomers. Preferably, the compounds of formula (I) are provided substantially free of the corresponding D-enantiomers, that is to say no more than about 5% w/w of the corresponding D-nucleoside, preferably no more than about 2% w/w, in particular less than about 1% w/w is present.

The compounds formula (I) include compounds in which the hydrogen of the 2-hydroxymethyl group and/or one or both of the hydrogens of a base amino group(s) is replaced by alkyl, alkenyl, aryl, a heteroaromatic group or a nonaromatic ring group, or are replaced by -C(O)R^6 or -C(O)OR^6 groups in which R^6 is alkyl, alkenyl, aryl optionally substituted by alkyl, a heteroaromatic group optionally substituted by alkyl, or a nonaromatic ring group.

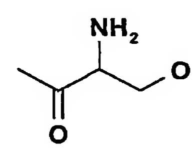
With regard to the compounds of formula (I), unless otherwise specified, any alkyl or alkenyl moiety present advantageously contains up to 20 carbon atoms, particularly 4 to 18 carbon atoms. Any aryl moiety present preferably contains 6 to 10 carbon atoms, for example, phenyl, napthyl, and biphenyl groups.

In the compounds of formula (I), R^1, R^3 and/or R^4 can also exhibit an amino acid radical or an amino acid chain.

Unless specified otherwise, the term "amino acid" used herein includes naturally-occurring amino acids as well as non natural analogs as those commonly used by those skilled in the art of chemical synthesis and peptide chemistry. A list of non natural amino acids may be found in "The Peptides", vol. 5, 1983, Academic Press, Chapter 6 by D.C. Roberts and F. Vellaccio. Example of naturally occurring amino acid includes alanine (Ala), arginine (Arg), asparagine (Asn), aspartic acid (Asp), cysteine (Cys), glutamine (Gln), glutamic acid (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), lysine (Lys), methionine (Met),

phenylalanine (Phe), ornithine (Orn), proline (Pro), serine (Ser), threonine (Thr), tryptophan (Trp), tyrosine (Tyr), and valine (Val). Preferably, the amino acid radical or amino acid chain exhibits at least one amino acid radical selected from Ala, Glu, Val, Leu, Ile, Pro, Phe, Tyr or Typ.

By the term "amino acid residue" and "amino acid chain residue" is meant an amino acid or amino acid chain preferably lacking the carboxy terminal hydroxyl group. For example, the amino acid residue of serine is preferably:



Pharmaceutically acceptable salts of the compounds of formula (I) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toleune-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g. magnesium), ammonium and NR_4+ (where R is C_{1-4} alkyl) salts.

The compounds of the invention either themselves possess anticancer activity and/or are metabolizable to such compounds.

By the term "amino acid chain" is meant two or more, prererably 2 to 6, amino acid residues covalently bound via a peptide or thiopeptide bond.

By the term "heteroaromatic" is meant an unsaturated ring structure containing 5 to 10 ring atoms wherein 1 to 3 ring atoms are each selected from N, O and S. Examples of heteroaromatic groups include but are not limited to:
furyl, thiophenyl, pyrrolyl, imidazolyl, pyrazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadrazolyl, thiadiazolyl, thiopyranyl, pyrazinyl, benzofuryl, benzothiophenyl, indolyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiozolyl, benzisothiazolyl, benzoxadiazolyl, quinolinyl, isoquinolinyl, carbazolyl, acridinyl, cinnolinyl and quinazolinyl.

Nonaromatic ring groups preferably contain 3-20 ring atoms in which 1-3 ring atoms are in each case selected from N, O and S. Preferred nonaromatic ring groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, piperazinyl, piperidinyl, morpholinyl,

thiomorpholinyl, pyrrolidinyl, adamantyl or quinuclidinyl.

The compounds of formula (I) include ester compounds. Such esters can be obtained by, for example, esterification of the 2-hydroxymethyl groups with a fatty acid. Typically fatty acids contain 4-22 carbon atoms. Examples of ester compounds of formula (I) include compounds in which at least one of R_1, R_3 or R_4 is acetyl, propionyl, butyryl, valeryl, caprioic, caprylic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, or linolenic.

There is thus provided as a further aspect of the invention, methods for treating solid tumors. A further aspect of the invention, is a method of treating liver cancer or metastasis thereof, lung cancer, renal cancer, colon cancer, pancreatic cancer, uterine cancer, ovarian cancer, breast cancer, bladder cancer, melanoma and lymphoma.

Compounds of the invention can be tested for use against cancers using any of a variety of art-recognized *in vitro* models [*e.g.*, inhibition of proliferation of cell lines such as tumor cell lines, as described herein and, for example, in Bowlin *et al.* (1998). *Proc. Am. Assn. for Cancer Res.* 39, #4147] or animal models [*e.g.*, leukemic (Gourdeau *et al.* (2000). *Cancer Chemotherapy and Pharmacology*) or solid tumor (Grove *et al.* (1997). *Cancer Res.*57: 3008-3011; Kadhim *et al.* (1997). *Cancer Res.*57: 4803-4810; Rabbani *et al.* (1998). *Cancer Res.*58: 3461; Weitman *et al.* (2000). *Clinical Cancer Res.*6: 1574-1578)] xenograft animal models. See, also, USP

5,817,667. Clinical tests of safety (absence of toxicity) and efficacy are carried out and evaluated using conventional testing methods.

Nucleosides can enter cells by any of a variety of mechanisms. As used herein, the term "nucleoside" means a nucleoside, nucleoside analog, modified nucleoside, or the like, for example any of the nucleoside "prodrugs" described above. Mechanisms of nucleoside uptake include, *e.g.*, uptake by nucleoside or nucleobase transporter proteins (NT), including sodium-independent, bidirectional equilibrative transporters such as, *e.g.*, the *es* or *ei* transporters; by sodium-dependent, inwardly directed concentrative transporters such as, *e.g.*, *cit*, *cib*, *cif*, *csg*, and *cs*; by nucleobase transporters; or by passive diffusion. For a discussion of the properties of some NTs, see, *e.g.*, Mackey *et al.* (1981). *Cancer Research* 58, 4349-4357 and Mackey et al. (1998). *Drug Resistance Updates* 1, 310-324, which are incorporated in their entirety by reference herein.

Methods (tests) for determining the mechanism(s) by which a nucleoside enters a cell are conventional in the art. Some such methods are described, *e.g.*, in Gourdeau *et al.* (2000). "Troxacitabine has an Unusual Pattern of Cellular Uptake and Metabolism that Results in Differential Chemosensitivity to Cytosine-Containing Nucleosides in Solid-Tumor and Leukemic Cell Lines" (submitted for publication and attached hereto as an appendix) and Paterson et al. (1991) "Plasma membrane transport of nucleosides, nucleobases and nucleotides: an overview," in Imai & Nakazawa, eds., Role of

adenosine and adenosine nucleotides in the biological system, Elsevier Science Publishers, which are incorporated in their entirety by reference herein. Typical methods include, for example:

1) NT inhibitor studies: measuring the ability of a nucleoside of interest to inhibit proliferation of cells, e.g., cancer (malignant) cells, or measuring the uptake of a labeled nucleoside of interest into a cell, wherein the nucleoside is administered to the cell in the presence or absence of one or more inhibitors of nucleoside transporters. Such inhibitors include, *e.g.*, NBMPR (nitrobenzylmercaptopurine), which is specific for the *es* transporter; dipyridamole, which is specific for the *es* and the *ei* NTs; and dilazep, which is specific for the NTs encoded by the genes hCNT1 and hCNT2, respectively. Reduction of activity or of uptake of a nucleoside of interest by an inhibitor of a particular NT implicates that NT in the mechanism of entry of the nucleoside into the cell; whereas the absence of such a reduction suggests that the NT is not involved. Methods to perform such assays are conventional and are disclosed, *e.g.*, in Mackey *et al.*, *supra* and in Examples 1-4.

2) Competition studies: measuring the kinetics of uptake of a labeled nucleoside which is known to be transported by a particular NT in the presence or absence of a large molar excess (*e.g.*, about a 100 to 1000-fold excess) of an unlabeled nucleoside of interest. If the nucleoside of interest competes with the labeled nucleoside for the NT, thereby reducing or abolishing the amount of uptake of the labeled nucleoside, this implicates that NT in the mechanism of

uptake of the nucleoside of interest. By contrast, the lack of such competition suggests that the NT is not involved in the uptake of the nucleoside of interest. See, *e.g.*, Example 31 (hCNT3 experiment). Cell proliferation studies such as those described above can also be studied by comparable competition assays.

3) Competition with uridine: measuring the kinetics of uptake of a labeled nucleoside of interest in the presence of a large molar excess (*e.g.*, about 100 to 1000-fold) of unlabeled uridine. Uridine is generally regarded as a "universal permeant," which can be taken up by cells by all of the reported human NTs. If a large excess of uridine does not inhibit the uptake of a nucleoside of interest, this indicates that the nucleoside is not transported by at least any of the currently known nuceoside transporters and, therefore, this is consistent with entry into the cell by passive diffusion.

4) Competition with the nucleoside of interest, itself: measuring the kinetics of uptake of a labeled nucleoside of interest in the presence or absence of a large molar excess (*e.g.*, about 100 to 1000-fold) of that nucleoside, itself, in unlabeled form. Reduction of the amount of labeled nucleoside taken up by a cell when excess unlabeled nucleoside is present suggests that a molecule with affinity for the nucleoside (*e.g.*, a nucleoside transporter) participates in the uptake mechanism. By contrast, unchanged or increased transport of the labeled nucleoside indicates that the mechanism of uptake is by passive diffusion. See, *e.g.*, Example 30 (HeLa cells; DU 145 cells), which demonstrates that uptake of ^{3}H-troxacitabine is not

inhibited by a large excess of unlabeled troxacitabine, indicating that the mechanism of uptake of troxacitabine in these cells is passive diffusion.

Any of the preceding tests can be carried out with any of a variety of cells which express a defined number of well-characterized nucleoside or nucleobase transporters. In addition to cell lines which naturally express defined numbers of NTs, mutant cell lines have been isolated which are deficient in one or more NTs, and/or one or more NTs can be introduced into a cell by conventional genetic recombinant methods. Genes encoding many NTs have been cloned (see, *e.g.*, Griffiths *et al.* (1997) *Nat. Med.* 3: 89-93; Crawford *et al.* (1998) *J. Biol. Chem.* 273: 5288-5293; Griffiths *et al.* (1997) *Biochem. J.* 328: 739-743; Ritzel *et al.* (1997) *Am. J. Physiol.* 272: C707-C714; Wang *et al.* (1997) *Am. J. Physiol* 273: F1058-F1065) or can be cloned by conventional methods; and methods of subcloning these genes into appropriate expression vectors are conventional. See, *e.g.*, Sambrook, J. *et al.* (1989). *Molecular Cloning, a Laboratory Manual.* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY for methods of cloning, subcloning, and expressing genes. A typical example of a panel of cell lines expressing different combinations of NTs is disclosed, *e.g.*, in Mackey *et al.*, *supra*.

5) Studies with artificial membranes, *e.g.*, reconstituted proteoliposomes comprising known NTs: measuring the kinetics of uptake of a labeled nuceoside of interest, e.g., in the presence or absence of inhibitors. See, *e.g.*, Mackey *et al.*, *supra*.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian.

In a preferred dosage regimen (regime, schedule), the compound a nucleoside analog of the invention) is administered to a patient at least daily for a period of about 2 to 10 consecutive days, preferably for about 3 to 7, more preferably for about 4 to 6, most preferably for about 5 days. This treatment is repeated, for example, every 2 to 5 weeks, preferably ever 3 to 4 weeks, particularly about every 4 weeks.

The amount of nucleoside analog to be administered using the above dosage regimen can be determined by conventional, routine procedures, *e.g.*, administering increasing amounts of the compound in order to determine the maximum tolerated dose.

For troxacitabine administration to a patient having a solid tumor, a preferred dosage range is about 1.2 to about 1.8 $mg/m^2/day$, more preferably about 1.5 $mg/m^2/day$. Sufficient time is allowed for the patient to recover from this treatment (*e.g.*, for the patient to recover an adequate white blood count to withstand another round of therapy). Generally the time for recovery is about 2-5 weeks. After the recovery period, another round of daily doses is administered as above.

A compound of the invention is preferably administered daily as described above about every 2 to 5 weeks, more preferably about every 3 to 4 or every 3 to 5 weeks. This dosage regimen can be repeated as necessary.

For troxacitabine administration to a patient having leukemia, higher amounts of the drug can be tolerated. The preferred dosage range for troxacitabine for this indication is about 3 to about 8 mg/m^2/day, preferably about 5 to about 8 mg/m^2/day, and most preferably about 8 mg/m^2/day. For treatment of leukemia, only one cycle of administration is generally required, although additional cycles can be administered, provided that the drug does not reach toxic levels.

Optimal dosages for any of the nucleoside analogs of the invention can be determined without undue experimentation. Using the daily dosage regimen (schedule) described above, one of skill in the art can routinely determine, using conventional methods, the maximum tolerable dosage for any of the nucleosides described herein. Optimal dosages will vary, of course, with parameters such as age, weight and physical condition of the patient, nature and stage of the disease, stability and formulation of the compound, route of administration, or the like. In general, because nucleosides modified with lipophilic substituents undergo more efficient passive diffusion through cell membranes than does troxicitabine, the dosages used for these nucleoside analogs can be lower than those for troxacitabine, for example, 10 to 100 fold lower.

Compounds of the invention can be administered, using the dosage regimens and dosage amounts discussed above, to any patient having cancer who would benefit from the treatment. For example, the patient to be treated can exhibit cancer cells that are resistant to one or more of other, commonly administered, anticancer drugs, *e.g.*, gemcitabine or ara-C (cytarabine). In another aspect, the malignant cells are deficient in nucleoside membrane transport via nucleoside or nucleobase transporter proteins, *e.g.*, they lack or comprise mutant forms of known nucleoside transporters such as, for example, *es*, *ei*, *cit*, *cib*, *cif*, *csg*, and *cs*. In another aspect, the drug (compound) enters the cancer cell predominantly (*e.g.*, at least about 50%) by passive diffusion.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical composition comprising a compound of formula **(I)** or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including

intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsiying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or

sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one more more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from presurrised packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebuliser or a pressurised pack or other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellant

such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a presurrised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compounds of the invention may also be used in combination with each other and/or with other therapeutic agents. In particular the compounds of the invention may be employed together with known anticancer agents.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt thereof together with

another therapeutically active agent, in particular an anticancer agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

Suitable therapeutic agents for use in such combinations include:

1) Alkylating agents such as:

- 2-haloalkylamines (e.g. melphalan and chlorambucil),
- 2-haloalkylsulfides,
- N-alkyl-N-nitrosoureas (e.g. carmustine, lomustine or
- semustine),
- aryltriazines (e.g. decarbazine),
- mitomycins (e.g. mitomycin C),
- methylhydrazines (e.g. procarbazine),
- bifunctional alkylating agents (e.g. mechlorethamine),
- carbinolamines (e.g. sibiromycin),
- streptozotocins and chlorozotocins,
- phosphoramide mustards (e.g. cyclophosphamide),
- urethane and hydantoin mustards,
- busulfan,
- oncovin;

2) Antimetabolites such as:

- mercaptopurines (e.g. 6-thioguanine and 6-[methylthio]purine),
- nucleoside (e.g.β-L-dioxolane cytidine),
- azapyrimidines and pyrimidines,
- hydroxyureas,
- 5-fluorouracil,
- folic acid antagonists (e.g. amethopterin),
- cytarabines,
- prednisones,
- diglycoaldehydes,
- methotrexate, and
- cytosine rabinoside;

3) Intercalators such as:

- bleomycins and related glycoproteins,
- anthracylines (e.g. doxorubicin, daunorubicin, epirubicin, esorubicin, idarubicin, aclacinomycin A),
- acridines (e.g. m-AMSA),
- hycanthones,
- ellipticines (e.g. 9-hydroxyellipticine),
- actinomycins (e.g. actinocin),
- anthraquinones (e.g. 1,4-bis[(aminoalkyl)-
- amino]-9,10-anthracenediones),
- anthracene derivatives (e.g. pseudourea and bisanthrene),
- phleomycins,
- aureolic acids (e.g. mithramycin and olivomycin), and

- Camptothecins (e.g. topotecan);

4) Mitotic inhibitors such as:
- dimeric catharanthus alkaloids
- vincristine, vinblastine and vindesine),
- colchicine derivatives (e.g. trimethylcolchicinic acid)
- epipodophyllotoxins and podophylotoxins
- etoposide and teniposide),
- maytansinoids (e.g. maytansine and colubrinol),
- terpenes (e.g. helenalin, tripdiolide and taxol),
- steroids (e.g. 4ß-hyroxywithanolide E),
- quassiniods (e.g. bruceantin),
- pipobroman, and
- methylglyoxals (e.g. methylglyoxalbis-(thiosemicarbazone);

5) Hormones (e.g. estrogens, androgens, tamoxifen, nafoxidine, progesterone, glucocorticoids, mitotane, prolactin);

6) Immunostimulants such as:
- human interferons, cytokines, levamisole and tilorane;

7) Monoclonal and polyclonal antibodies;

8) Radiosensitizing and radioprotecting compounds such as:
- metronidazole and misonidazole;

9) Other miscellaneous cytotoxic agents such as:
   - camptothecins,
   - quinolinequinones,
   - streptonigrin and isopropylidene azastreptonigrin),
   - cisplatin, cisrhodium and related platinum series complexes,
   - tricothecenes (e.g. trichodermol or vermicarin A), and
   - cephalotoxines (e.g. harringtonine);

10) Enzymes, such as
   - L-asparaginase;

11) Drug-resistance reversal compounds such as P-glycoprotein inhibitors, for example Verapamil, cyclosporin-c, and fujimycin;
12) Cytotoxic cells such as lymphokine activated killer -cells or T-cells;
13) Other Immunostimulants such as interleukin factors or antigens;
14) Polynucleotides of sence or antisensing nature;
15) Polynucleotides capable of forming triple helices with DNA or RNA;
16) Polyethers;
17) Distamycin and analogs;
18) Taxanes such as taxol and taxotere; and
19) Agents that are protective against drug induced toxicities such as granulocyte macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF).

The above list of possible therapeutic agents is not intended to limit this invention in any way. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I), or a pharmaceutically acceptable salt thereof is used in combination with a second therapeutic agent the dose of each compound may be either the same as or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compounds of formula (I) and their pharmaceutically acceptable salts may be prepared by any method known in the art for the preparation of compounds of analogous structure, for example as described in international application No PCT/CA92/00211 published under No Wo 92/20669 which is herein incorporated by reference.

Certain intermediates useful in the synthesis of the compounds of the present invention can be synthesized as generally described in J.Med.Chem. 1994, 37, 1501-1507, Lyttle et al.

It will be appreciated by those skilled in the art that for certain of the methods the desired stereochemistry of the compounds of formula (I) may be obtained either by commencing with an optically pure starting material or by resolving the racemic mixture at any convenient stage in the synthesis. In the case of all the processes the optically pure desired product may be

obtained by resolution of the end product of each reaction.

It is also possible to resolve the final compound using chiral HPLC (high pressure liquid chromatography) as it is well known in the art.

Brief Description of the Drawings

Various other features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood when considered in conjunction with the accompanying figures, wherein:

Fig. 1 Comparative uptake of 30 μM [^{3}H]-troxacitabine in CEM (Panel A) and CEM/ARAC8C (Panel B) cells. [^{3}H]-Uridine uptake in either the presence or absence of the hENT1 inhibitor, NBMPR or 5 mM non-radioactive uridine was included for comparison as a control substrate. Each data point represents the mean (± standard deviation) of three determinations.

Fig. 2 Comparative uptake of 10 μM [^{3}H]troxacitabine (0-240 min) (Panel B) and 10 μM [^{3}H]D-uridine (0-6 min) (Panel A) in the presence (▲) or absence (Π) of the hENT1 inhibitor, 100 nM NBMPR, in DU145 cells. Each data point represents the mean (± standard deviation) of three determinations.

Fig. 3 Comparative uptake of 10 μM [^{3}H]troxacitabine and 10 μM [^{3}H]D-uridine in HeLa cells. A. Uptake of [^{3}H]troxacitabine (Π) and [^{3}H]D-uridine (Θ) in the presence of the hENT1 inhibitor, 100 nM NBMPR using a scale of 0-1500 pmol/10^6 cells. B.Uptake of

[^{3}H]troxacitabine either in the absence (Π) or presence of 100 nM NBMPR (▲), 100 μM dilazep (▼), 1 mM non-radioactive troxacitabine (♦) or 20 μM dipyridamole (•), using an expanded scale of 0-15 pmol/10^6 cells. Each data point represents the mean (± standard deviation) of three determinations.

Fig. 4 Comparative uptake of 10 µM [^{3}H]troxacitabine and 10 µM [^{3}H]D-uridine in HeLa cells transiently transfected with recombinant pcDNA3 containing either the coding sequence for: (A) hCNT1 or (B) hCNT2. Transport assays were conducted in the presence of the equilibrative transport inhibitor, 100 μM dilazep and either in the presence (Π) or absence (▲) of with the empty vector control plasmid (▼).sodium, and compared to HeLa cells transiently transfected with the empty vector control plasmic (▼).

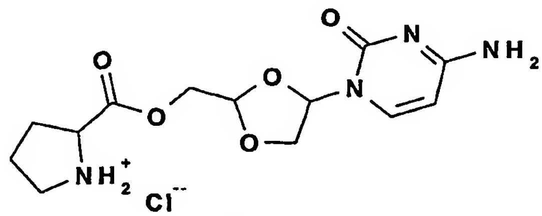
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

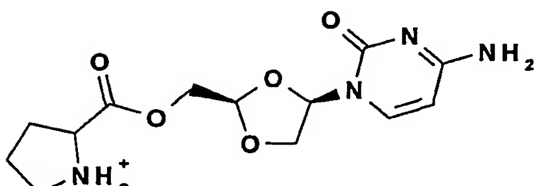
The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

EXAMPLE 1

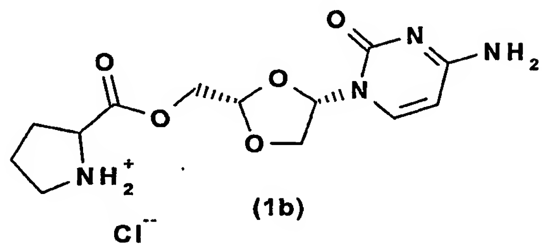
Preparation of 2-(prolyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride (1, 1a, and 1b)



(1)



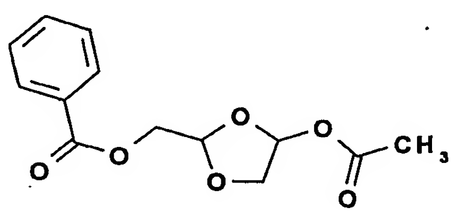
(1a)



(1b)

STEP 1

Preparation of 4-Acetoxy-2-(O-Benzoyloxymethyl)-dioxolane



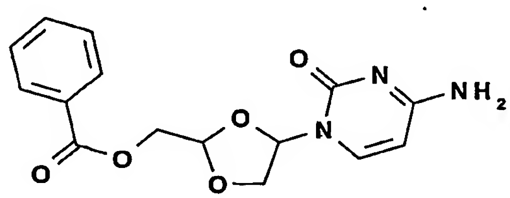
A mixture .of Benzyl-1,2-Dihydroxy Butyrate (116 mg; 0.97 mmol), Benzoyloxybenzaldehyde (159mg; 0.97 mmol) and ρ-toluene sulfonic acid (9mg; 0.047 mmol) in dry benzene (25ml) under argon is heated at reflux for 4 h. Solvent is then removed under reduced pressure and the remaining solid is worked-up by washing with 5% sodium

bicarbonate. A purification of the crude material by chromatography on silica gel gives the expected benzyl ester. The resulting compound is dissolved in ethanol (25ml) and treated with Pd/C (excess) under hydrogen atmosphere overnight. Filtration of the catalyst and evaporation of the solvent affords the expected deprotected acid.

Lead acetate (146mg; 0.34mmol) and pyridine (0.03ml, 0.33mmol) are added to a solution of the crude solid (90mg; 0.33mmol) in dry tetrahydrofuran (THF) (25ml) under argon atmosphere. The mixture is stirred for 4 h under argon and the solid is removed by filtration. The crude material is washed with ethyl acetate(EtOAc) and purified by chromatography on silica gel. This affords the pure dioxolane derivative.

STEP 2

Preparation of 1-[2-benzoyloxy methyl-1,3-dioxolan-4-yl] cytosine.



A mixture of N^4-acetylcytosine (124mg; 0.75mmol), dry hexamethyl disilazane (20ml) and ammonium sulfate (2-3mg; catalyst) is refluxed for 5 h. under an argon atmosphere. The clear solution is cooled to room temperature and the solvent evaporated under reduced pressure. The resulting residue is dissolved in dry

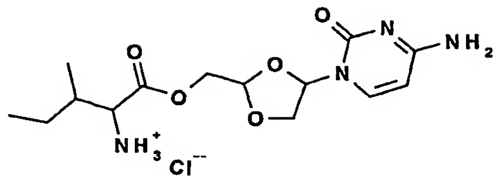
dichloromethane (15ml). A solution of the dioxolane derivative obtained in step 1 (102mg; 0.55mmol) in dry dichloromethane (10ml) and iodotrimethyl silane (0.076ml; 0,54mmol) is added to the silylated cytosine. The resulting mixture is stirred for 4 h. and worked-up by treating the solution with a 5% solution of sodium bicarbonate. The solvent of the resulting organic layer is evaporated under reduced pressure. The crude material is purified by chromatography on silica gel to give the expected nucleoside derivative.

STEP 3

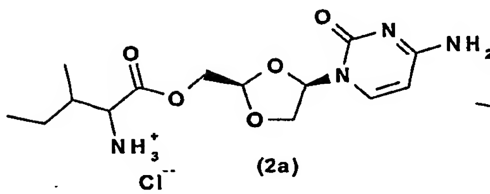
1-[2-hydroxymethyl-1,3-dioxolan-4-yl] N-[(dimethylamino)methylene] cytosine (268 mg; 1mmol) is dissolved in dichloromethane (10 ml). To this solution is added dicyclohexylcarbodiimide (206 mg; 1 mmol); 4-(dimethylamino)-pyridine (12 mg; 0.1 mmol); and Boc-proline (215 mg; 1mmol) at 0°C. The reaction is stirred at this temperature overnight. Insoluble is filtered off and the solvent is evaporated to dryness. The solid is redissolved in dry ether (15 ml) and the solution is bubbled with HCl gas at 0°C for ten minutes. The reaction is kept at room temperature for 2 h.. The white precipitate is filtered and dried.

EXAMPLE 2

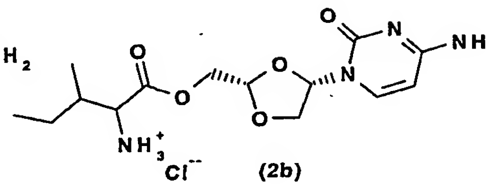
Preparation of 2-(isoleucinyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride salt (2, 2a, and 2b)



(2)



(2a)

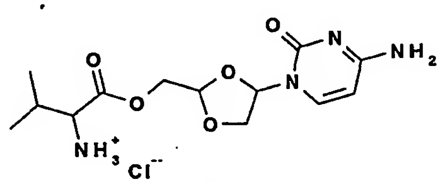


(2b)

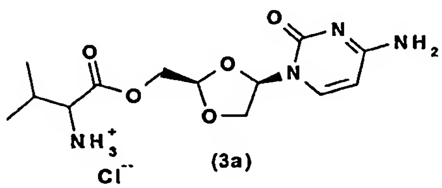
The above compound is synthesized according to the procedure described in example 1 except that proline is replaced by isoleucine.

EXAMPLE 3

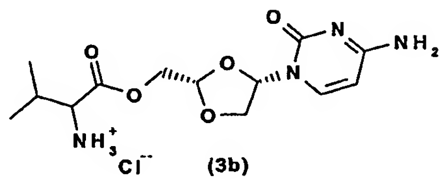
Preparation of 2-(leucinyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride salt (3, 3a, and 3b)



(3)



(3a)

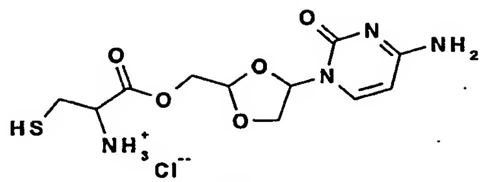


(3b)

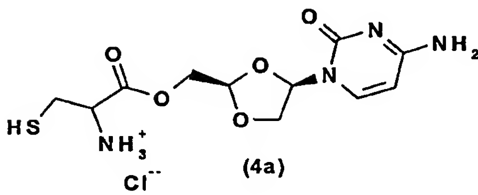
The above compound is synthesized according to the procedure described in example 1 except that proline is replaced by leucine.

EXAMPLE 4

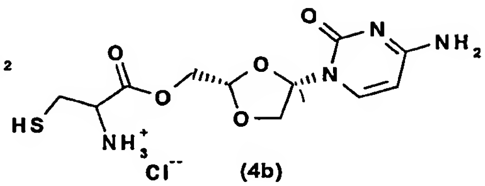
Preparation of 2-(cysteinyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride salt (4, 4a, and 4b)



(4)



(4a)

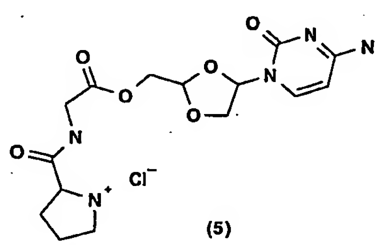


(4b)

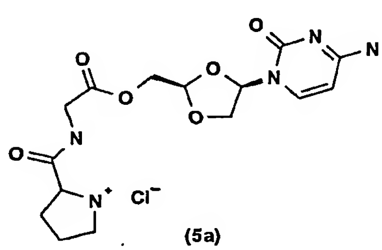
The above compound is synthesized according to the procedure described in example 1 except that proline is replaced by cysteine.

EXAMPLE 5

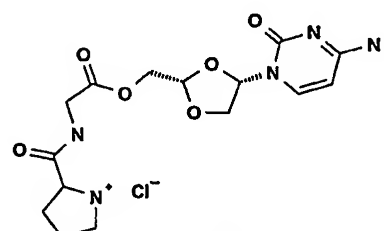
Preparation of 2-(prolylglycinyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride salt (5, 5a, and 5b)



(5)



(5a)

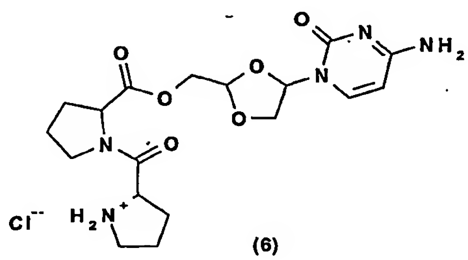


(5b)

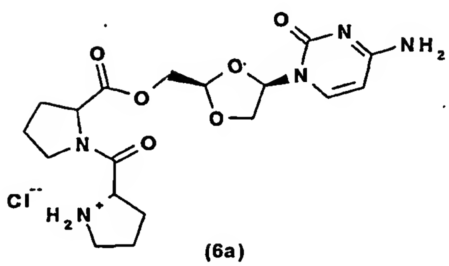
The compound is synthesized according to the procedure described in example 1 except that proline is replaced by prolylglycine.

EXAMPLE 6

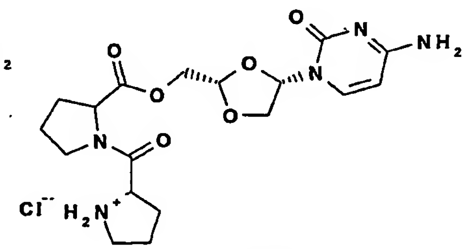
Preparation of 2-(prolylprolynyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride salt (6, 6a, and 6b)



(6)



(6a)

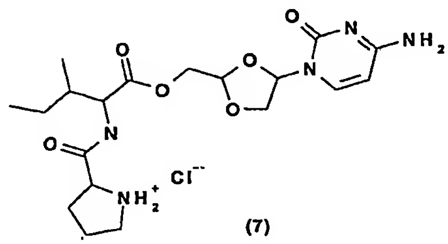


(6b)

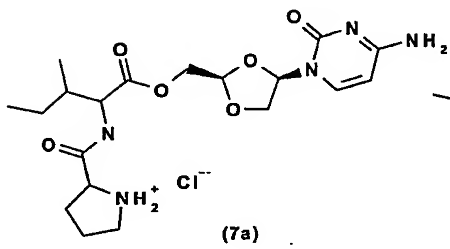
The above compound is synthesized according to the procedure described in example 1 except that proline is replaced by prolylproline.

EXAMPLE 7

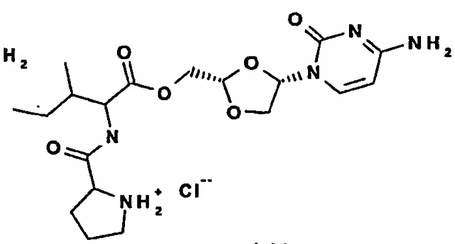
Preparation of 2-(prolylleucinyloxymethyl)-4-cytosin-1''-yl-1,3-dioxolane hydrochloride salt (7 7a, and 7b)



(7)



(7a)

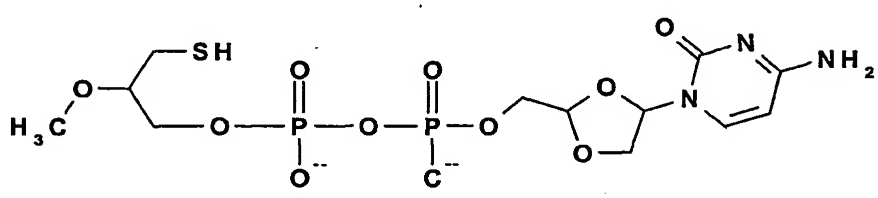


(7b)

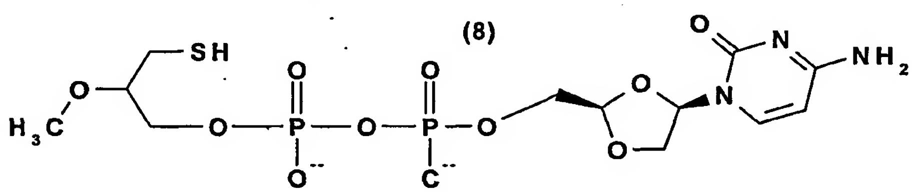
The above compound is synthesized according to the procedure described in example 1 except that proline is replaced by prolylleucine.

EXAMPLE 8

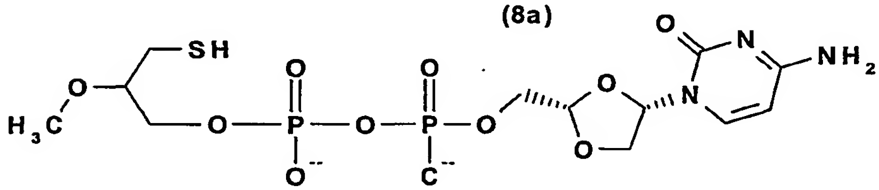
Preparation of 2-(1'-methylthio-2'-O-methyl-3'glycerolphosphonate)- 4-cytosin-1''-yl-1,3-dioxolane (8 8a, and 8b)



(8)



(8a)



(8b)

Step 1

Preparation of 1-methylthio-2-O-methyl-3 glycerolphosphonate

CH_2SCH_3

|

$CHOCH_3$

|

$CH_2OP(O)(OH)_2$

To an ice-cold mixture of Phosphorus oxychloride (445 mg; 2.9 mmol) and hexanes (5 ml) is added dropwise triethyl amine (295.35 mg; 2.9 mmol) in hexanes (5 ml). To this mixture is added dropwise a solution of dried 1-methylthio-2-O-methyl 3-glycerol (98 mg; 1.9 mmol) in toluene (100 ml) at 0-5°C over a period of 1.5 h, and then the mixture is stirred at room temperature overnight. Water is added to the mixture and the organic layer is evaporated to give the desired product.

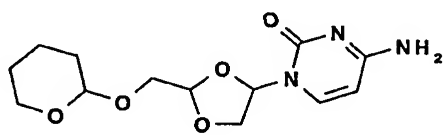
Step 2

Preparation of 2-(1'-methylthio-2'-O-methyl-3'glycerolphosphonate)- 4-cytosin-1''-yl-1,3-dioxolane (8 8a, and 8b)

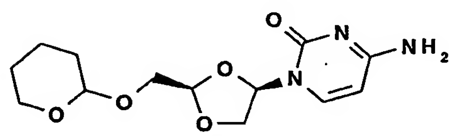
The phosphonate prepared in the first step (242 mg; 0.39 mmol) is dissolved in pyridine (10 ml). To this solution is added the dioxolane monophosphate morpholidate (198 mg; 0.31 mmol) and the mixture is stirred at room temperature for three days. Solvent is evaporated and the residue was purified by ion exchange column.

EXAMPLE 9

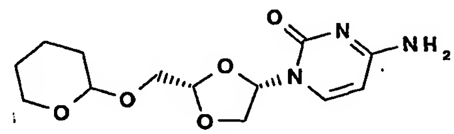
Preparation of 4-cytosin-1''-yl-1,3-dioxolane-2-(tetrahydropyranylmethyl) ether (9 9a, and 9b)



(9)



(9a)

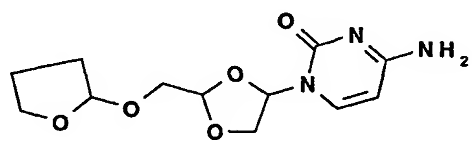


(9b)

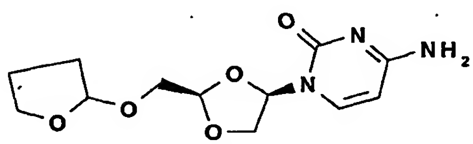
A mixture of cytosine nucleoside (684 mg; 1.9 mmol), 3,4-dihydro-2H-pyran (336 mg; 4 mmol), and p-toluene sulfonic acid (38 mg; 0.19 mmol) in dichloromethane (20 ml) is stirred for 3 h. Solvent is removed under reduced pressure and the residue is purified by chromatography.

EXAMPLE 10

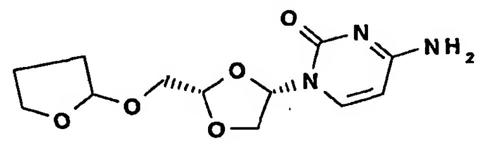
Preparation of 4-cytosin-1''-yl-1,3-dioxolane-2-(tetrahydrofuranylmethyl) ether (10 10a, and 10b)



(10)



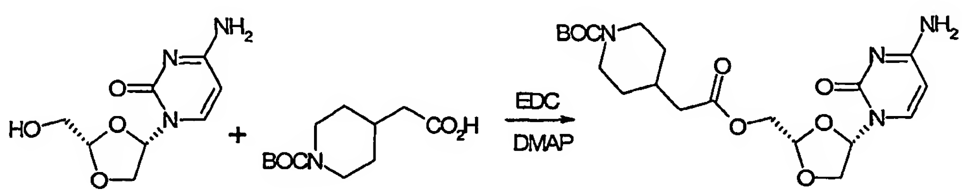
(10a)



(10b)

The above compound is synthesized according to the procedure described in example 9 except that 3,4-dihydro-2H-pyran is replaced by Ph_2CHCO_2-2-tetrahydrofuranyl.

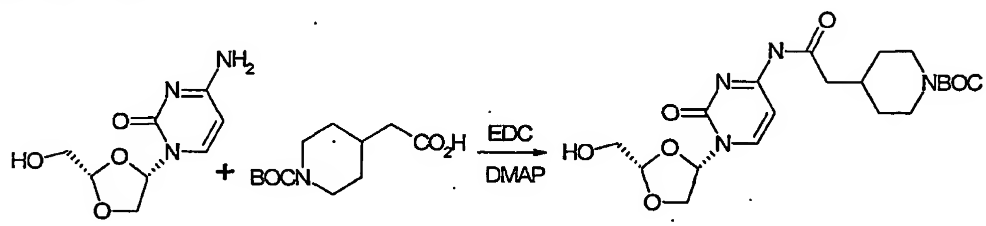
EXAMPLE 11



Procedure: EDC (407 mg, 2.12 mmol, 1.0eq) and DMAP (27 mg, 0.21mmol, 0.1eq) were added to a suspension of the nucleoside (451 mg, 2.12 mmol, 1.0eq) and the acid (486 mg, 2.12mmol, 1.0eq) in DMF (10 mL) and the clear mixture stirred over night at room temperature. All

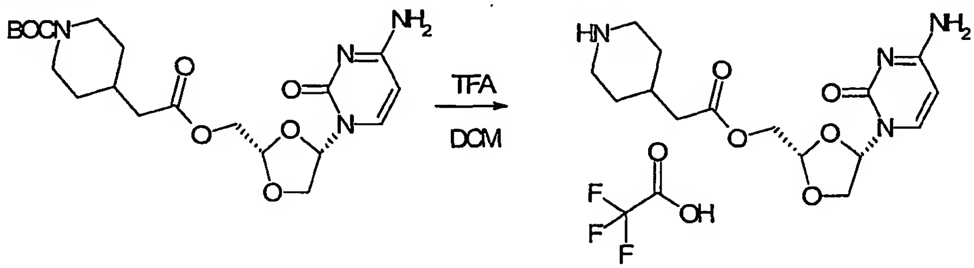
solvent was evaporated to dryness and residue purified by chromatography (from 100% ethyl acetate to 15% methanol in ethyl acetate) 385 mg of ester was recovered.

EXAMPLE 12



Procedure: EDC (407 mg, 2.12 mmol, 1.0eq) and DMAP (27 mg, 0.21mmol, 0.1eq) were added to a suspention of the nucleoside (451 mg, 2.12 mmol, 1.0eq) and the acid (486 mg, 2.12mmol, 1.0eq) in DMF (10 mL) and the clear mixture stirred over night at room temperature. All solvent was evaporated to dryness and residue purified by chromatography (from 100% ethyl acetate to 15% methanol in ethyl acetate) 85 mg of amide was recovered.

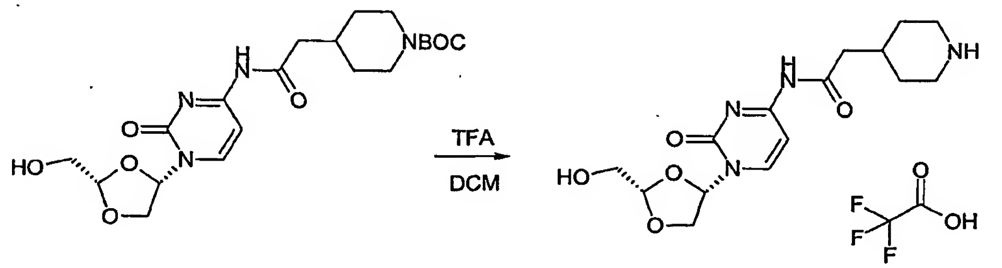
EXAMPLE 13



Procedure: TFA (3 mL) was added to a dichloromethane solution (7 mL) of BOC protected compound (124 mg, 0.28 mmol) and stirred for 2 hours. All solvent was evaporated to dryness. The crude was redissolved in minimal amount of methanol (0.5 mL) and slowly added to ether (10 mL) with strong agitation. The supernatant was removed and the solid dried under vacuum. 125 mg was isolated.

^{1}H NMR (400 MHz, DMSO-d6): 8.50 (br s, 1H), 8.25 (br s, 2H), 7.80 (d, J=7.5Hz, 1H), 6.23 (d, J=4.0Hz, 1H), 6.01 (d, J=8.0Hz, 1H), 5.19 (t, J=3.0Hz, 1H), 4.35-4.25 (m, 3H), 4.16 (m, 1H), 3.25 (d, J=13.5Hz, 2H), 2.88 (q, J=11.0Hz, 2H), 2.36 (d, J=7.0Hz, 2H), 1.95 (m, 1H), 1.81 (d, J=13.0Hz, 2H), 1.33 (q, J=10.0Hz, 2H).

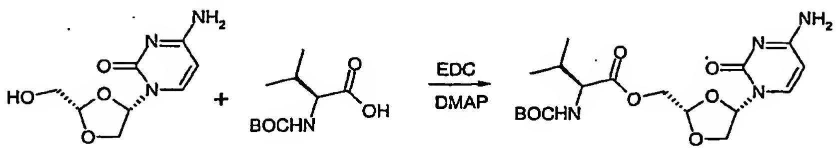
EXAMPLE 14



Procedure: TFA (3 mL) was added to a dichloromethane solution (7 mL) of BOC protected compound (81 mg, 0.19 mmol) and stirred for 2 hours. All solvent was evaporated to dryness. The crude was redissolved in minimal amount of methanol (0.5 mL) and slowly added to ether (10 mL) with strong agitation. The supernatant was removed and the solid dried under vacuum. 54 mg was isolated.

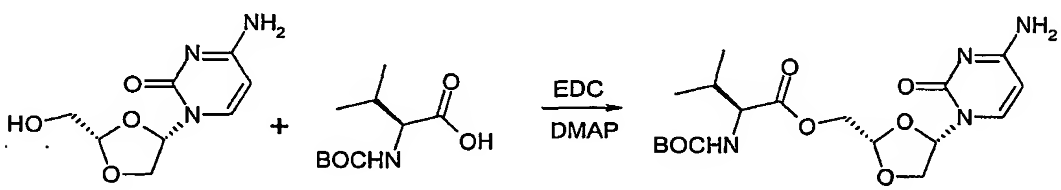
^{1}H NMR (400 MHz, DMSO-d6): 10.92 (s, 1H), 8.50 (br s, 1H), 8.38 (d, J=7.5Hz, 1H), 8.15 (br s, 1H), 7.22 (d, J=7.5Hz, 1H), 6.15 (m, 1H), 5.00 (s, 1H), 4.17 (d, J=4.5Hz, 2H), 3.71 (s, 2H), 3.24 (d, J=12.0Hz, 2H), 2.89 (q, J=8.5Hz, 2H), 2.39 (d, J=7.0Hz, 2H), 2.00 (br s, 1H), 1.79 (d, J=14.0Hz, 2H), 1.34 (q, 12.0Hz, 2H).

EXAMPLE 15



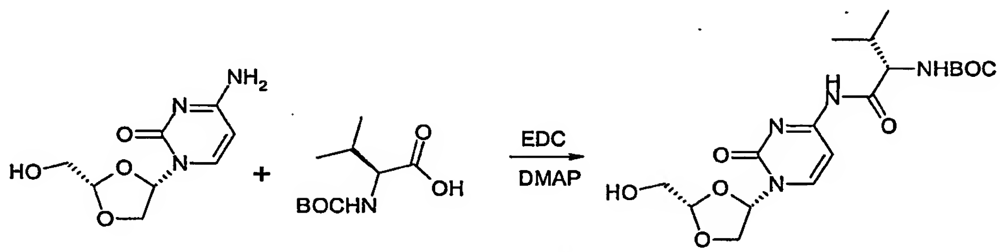
Procedure: EDC (512 mg, 2.67 mmol, 1.0eq) and DMAP (34 mg, 0.27 mmol, 0.1eq) were added to a suspention of the nucleoside (568 mg, 2.67 mmol, 1.0eq) and the acid (565 mg, 2.67 mmol, 1.0eq) in DMF (10 mL) and the clear mixture stirred over night at room temperature. All solvent was evaporated to dryness and residue purified by chromatography (from 100% ethyl acetate to 15% methanol in ethyl acetate) 355 mg of ester was recovered.

EXAMPLE 16



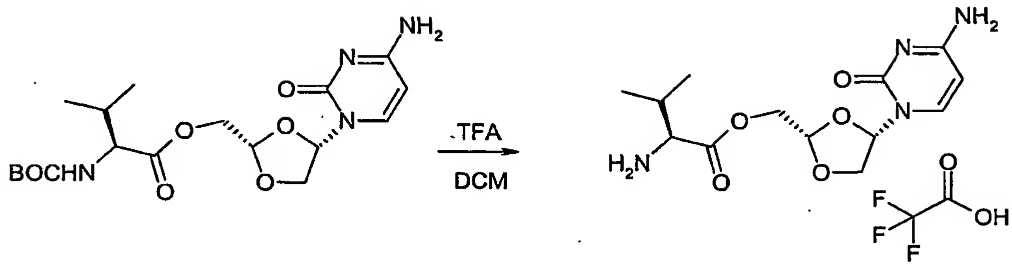
Procedure: EDC (512 mg, 2.67 mmol, 1.0eq) and DMAP (34 mg, 0.27 mmol, 0.1eq) were added to a suspention of the nucleoside (568 mg, 2.67 mmol, 1.0eq) and the acid (565 mg, 2.67 mmol, 1.0eq) in DMF (10 mL) and the clear mixture stirred over night at room temperature. All solvent was evaporated to dryness and residue purified by chromatography (from 100% ethyl acetate to 15% methanol in ethyl acetate) 355 mg of ester was recovered.

EXAMPLE 17



Procedure: EDC (512 mg, 2.67 mmol, 1.0eq) and DMAP (34 mg, 0.27 mmol, 0.1eq) were added to a suspention of the nucleoside (568 mg, 2.67 mmol, 1.0eq) and the acid (565 mg, 2.67 mmol, 1.0eq) in DMF (10 mL) and the clear mixture stirred over night at room temperature. All solvent was evaporated to dryness and residue purified by chromatography (from 100% ethyl acetate to 15% methanol in ethyl acetate) 102 mg of amide was recovered.

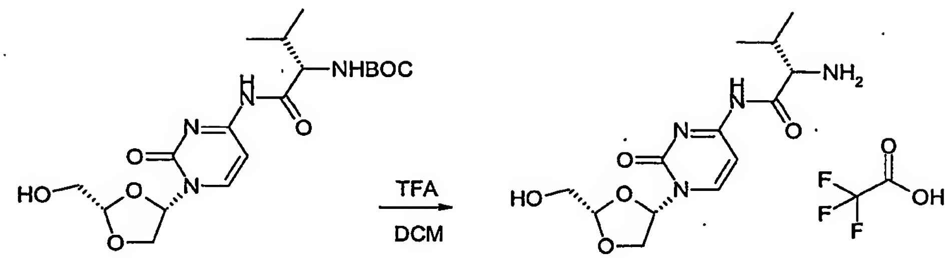
EXAMPLE 18



Procedure: TFA (3 mL) was added to a dichloromethane solution (7 mL) of BOC protected compound (127 mg, 0.31 mmol) and stirred for 2 hours. All solvent was evaporated to dryness. The crude was redissolved in minimal amount of methanol (0.5 mL) and slowly added to ether (10 mL) with strong agitation. The supernatant was removed and the solid dried under vacuum. 111 mg was isolated.

^{1}H NMR (400 MHz, DMSO-d6): 8.40 (br s, 2H), 8.15 (br s, 1H), 7.75 (d, J=7.5Hz, 1H), 6.27 (d, J=4.0Hz, 1H), 6.00 (d, J=7.5Hz, 1H), 5.23 (t, J=3.5Hz, 1H), 4.49 (qd, J=12.0Hz, J=3.0Hz, 2H), 4.29 (d, J=10.0Hz, 1H), 4.19 (m, 1H), 4.04 (s, 1H), 2.14 (m, 1H), 0.95 (D, J=7.0Hz, 6H).

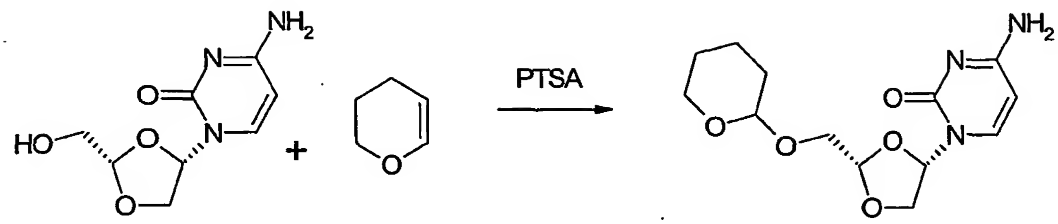
EXAMPLE 19



Procedure: TFA (3 mL) was added to a dichloromethane solution (7 mL) of BOC protected compound (100 mg, 0.24 mmol) and stirred for 2 hours. All solvent was evaporated to dryness. The crude was redissolved in minimal amount of methanol (0.5 mL) and slowly added to ether (10 mL) with strong agitation. The supernatant was removed and the solid dried under vacuum. 54 mg was isolated.

^1H NMR (400 MHz, DMSO-d6): 8.48 (d, J=7.5Hz, 1H), 8.25 (br s, 3H), 7.17 (d, J=7.5Hz, 1H), 6.16 (d, J=4.0Hz, 1H), 5.29 (m, 1H), 5.03 (t, J=2.5Hz, 1H), 4.25-4.15 (m, 2H), 3.90 (s, 1H), 3.72 (s, 2H), 2.18 (m, 1H), 0.95 (m, 6H).

EXAMPLE 20



Procedure: Paratoluene sulfonic acid (82mg, 0.43 mmol, 1.0eq.) was added to asolution of BCH-4556 (92mg, 0.43mmol, 1.0eq.) in DMF (1mL) and 3,4-dihydropyran (3mL). The reaction was stirred for 16 hours and potassium carbonate (119mg, 0.86mmol, 2.0eq.) added and stirred for 1 hour. The solid was filtered off and the solvent evaporated to dryness. The crude was purified by flash using a gradient of 5 to 10% methanol in dichloromethane. 100mg of desired compound was isolated.

^{1}H NMR (400 MHz, DMSO-d6): 7.79 (t, J=8.0hz, 1H), 7.18 (br d, J=20.0hz, 2H), 6.20 (m, 1H), 5.71 (d, J=7.0hz, 1H), 5.09 (m, 1H), 4.68 (m, 1H), 4.09 (m, 2H), 3.86 (m, 1H), 3.80-3.65 (m, 2H), 3.48 (m, 1H), 1.80-1.60 (m, 2H), 1.60-1.45 (m, 4H).

EXAMPLE 21

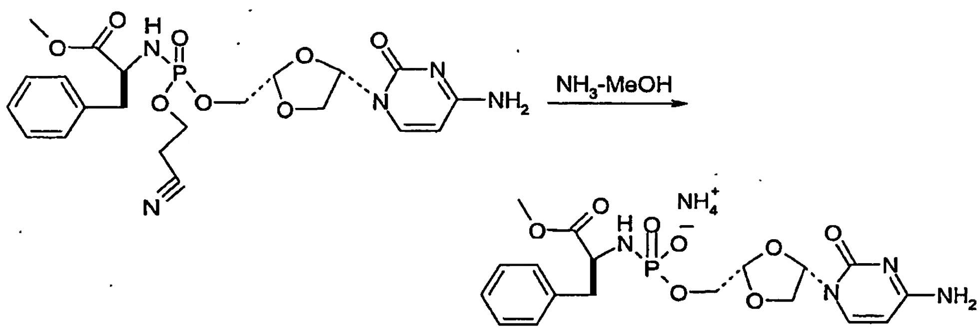
Preparation of Cis-L-2-[2''-cyanoethyl methoxy- L-phenylalaninylphosphoroamidyloxymethyl-4-(cytosin-1'-yl)]-1,3-dioxolane

Procedure: Dry BCH 4556(dimethylaminomethylene derivative, 0.1 g, 0.373 mmol) was dissolved in dry DMA (2 ml) under nitrogen and cooled in an ice bath. Diisopropylethylamine(0.2 ml) and 2,cyanoethyl-N,N-diisopropylchlorophosphoramidite (0.17 ml, 1.12 mmol) were added in respective order. After 1 hour [1]Tetrazole (0.1 g, 1.49 mmmol) was added and after 10 minutes dry methanol (0.05 ml) was introduced. The reaction mixture was allowed to warm to room temperature over 2 hours. L-phenylalanine methyl ester (hydrochloride, 0.39 g, 2.18 mmol) and iodine (0.19 g, 0.746 mmol) were added in respective order. Combined mixture was allowed to stir for 2 hours and excess iodine was quenched with saturated sodium thiosulphate solution. It was evaporated to dryness and the residue was extracted with dichloromethane, washed with brine and dried over an hydrous $MgSO_4$. After evaporation the crude product was purified on a flash silica gel column which was eluted with a mixture of dichloromethane and methanol (ratio 10:1). Tare of the title compound was 0.072 g.

^{1}H-NMR (400 MHz, $CDCl_3$): δ:7.95(1H, d); 6.7(1H, dd); 6.2(1H, dd); 5.01(1H,s); 4.9-2.5 (m, 14H) ppm.

Appearance oil

Ref. Abraham, T.W.; Wagner, C.R. Nucleosides &

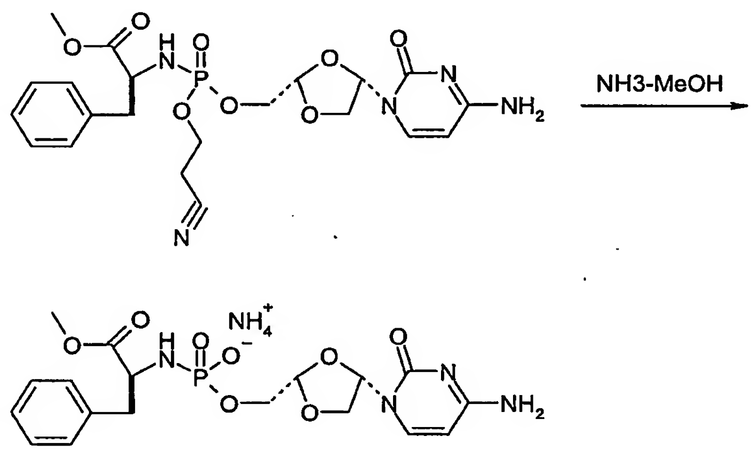


Nucleotides, 13(9), 1891-1903 (1994)

EXAMPLE 22

Preparation of Cis-L-2-methoxy-L-phenylalaninylphosphoro-amidyloxymethyl-4-(cytosin-1'-yl)]-1,3-dioxolane Ammonium salt

Ref Abraham, T.W.; Wagner, C.R. Nucleosides & Nucleotides, 13(9), 1891-1903 (1994)



Appearance Foam

Procedure: Dry Cis-L-2-[2''-cyanoethyl methoxy- L-phenylalaninylphosphoroamidyloxymethyl-4-(cytosin-1'-yl)]-1,3-dioxolane (0.072g, 0.128 mmol) was dissolved in dry methanol (9.7 ml) and mixed with a saturated solution of ammonia in dry methanol (5.8 ml). Combined mixture was allowed to stir for 1 hour. Solvent was evaporated and the crude product was purified ona silica gel column which was eluted with a mixture of dichloromethane and methanol (ratio 2:1). Tare of the title compound was 0.031g.

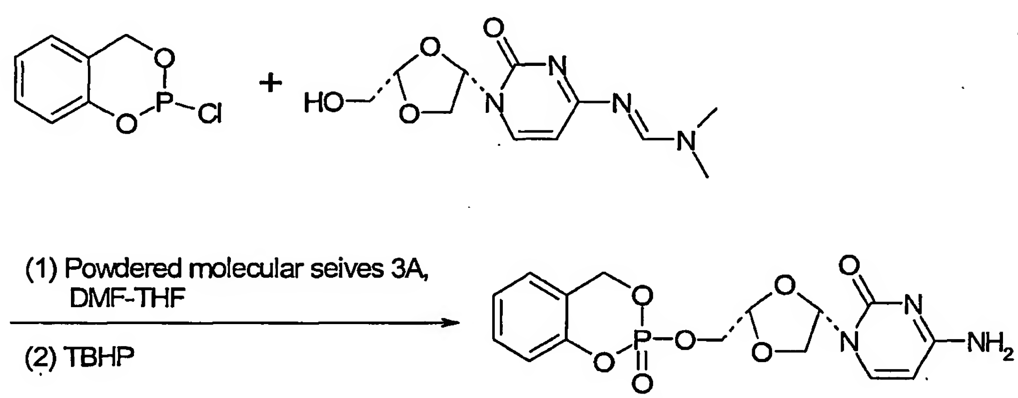
^{1}H NMR(400 MHz, CD_3OD) δ: 8.15(1H,d); 7.2(5H,m); 6.25(1H,t); 6.05(1H,d); 5.08(1H,s); 4.05(5H,m); 3.55(3H,s); 3.0(2H,qq) ppm.

UV: λ_{max}(MeOH) 272 nm.

MS: m/e 453.2

EXAMPLE 23

Preparation of Cis-1-Cyclosaligenyl-2-oxymethyl-[(4-cytosin-1'-yl)-1,3-dioxolane]-phosphate diastereomers



Procedure: Dry BCH 4556(dimethylaminomethylene derivative, 0.05g, 0.1865 mmol) was dissolved in dry DMF (2 ml) and dry THF (1 ml). It was cooled to -40° C in an argon atmosphere. Freshly activated powdered molecular sieves (0.05g) were added. Cyclic saligenylchloroposphanes (0.071g, 0.373 mmol) was dissolved in dry THF (0.5 ml) and introduced over 30 minutes. Combined mixture was stirred at -40° C for another half an hour. Tert-Butylhydroproxide (3 M solution in 2,2,4-trimethylpentane, 0.125 ml) was

added. After stirring for half an hour, the reaction mixture was allowed to wam to room temperature. The solvent was evaporated and the crude product was extracted with ethyl acetate. It was purified on a silica gel column using a mixture of ethyl acetate and methanol (ratio 5:2). Further purification and the separation of diastereomers was carried on reverse phase HPLC.

^{1}H NMR(400MHZ, DMSO-D6)δ : 8.25(1H,d); 7.4(5H,m); 6.15(1H,t); 5.75(1H,d), 5.5(2H,m); 5.2(1H,s); 4.2(4H,m) ppm.

UV : λ_{max} (MeCN) 277nm

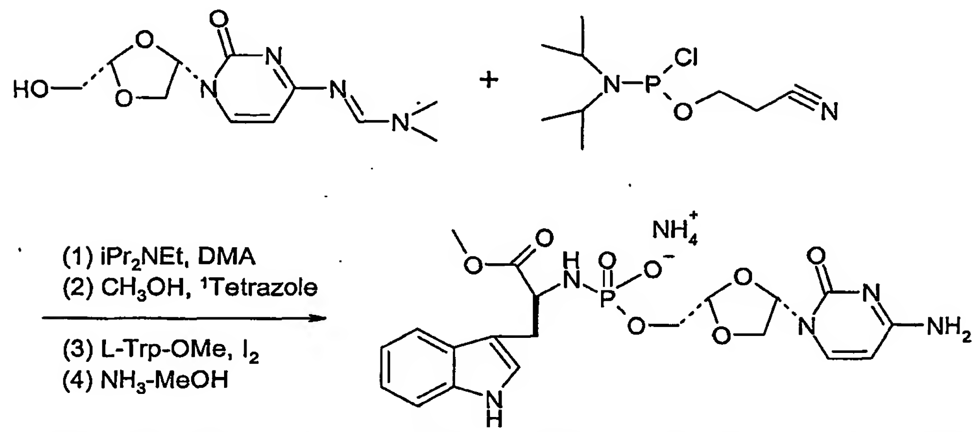
MS : m/e 381

Ref Meier,C.; Knispel,T.; Marquez,V.E.; Siddiqui,M.A.; De Clercq,E.; Balzarini,J. J.Med.Chem. **1999**, 42, 1615-1624.

Appearance Foam

EXAMPLE 24

Preparation of Cis-L-2-methoxy-L-tryptophanyl1phosphoroamidyl oxy methyl-4-(cytosin-1'-yl)]-1,3-dioxolane Ammonium salt



Procedure: Dry BCH 4556 (dimethylaminomethylene derivative, 0.16 g, 0.597 mmol) was dissolved in dry DMA (3.2 ml) under nitrogen and cooled in an ice bath. Diisopropylethylamine(0.32 ml) and 2,cyanoethyl-N,N-diisopropylchlorophosphoramidite (0.27 ml, 1.79 mmol) were added in respective order. After 1 hour [1]Tetrazole (0.16 g, 2.38 mmmol) was added and after 10 minutes dry methanol (0.08 ml) was introduced. The reaction mixture was allowed to warm to room temperature over 2 hours. L-tryptophan methyl ester (hydrochloride, 0.74 g, 3.5 mmol) and iodine (0.32 g, 1.2 mmol) were added in respective order. Combined mixture was allowed to stir for 2 hours and excess iodine was quenched with saturated sodium thiosulphate solution. It was evaporated to dryness and the residue was extracted with dichloromethane, washed with brine and dried over an hydrous $MgSO_4$. After evaporation the

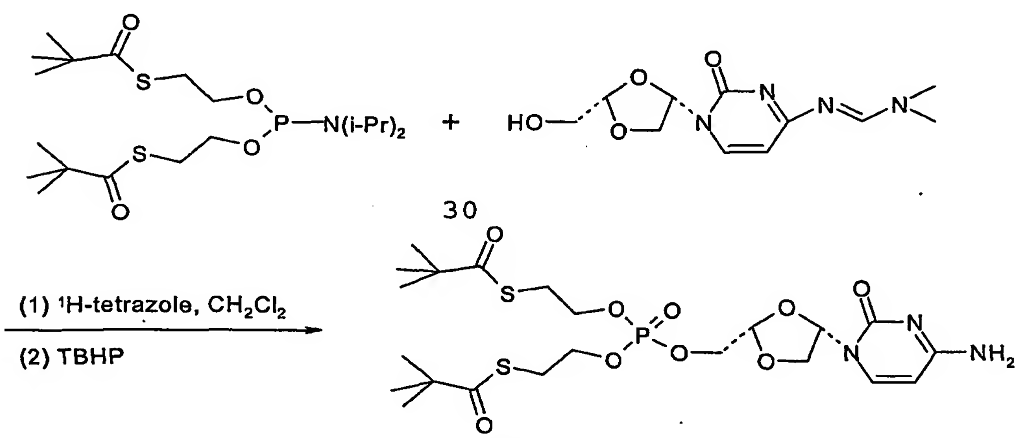
crude product was purified on a flash silica gel column which was eluted with a mixture of dichloromethane and methanol (ratio 5:1).

The product was dissolved in dry methanol (15 ml) and mixed with a saturated solution of ammonia in dry methanol (9.3 ml). Combined mixture was allowed to stir for 1 hour. Solvent was evaporated and the crude product was purified on a silica gel column which was eluted with a mixture of dichloromethane and methanol (ratio 2:1). Tare of the title compound was 0.016 g.

^{1}H NMR(400 MHz, CD_3OD) δ: 8.1(1H,d); 7.2(5H,m); 6.2(1H,t); 5.95(1H,d); 5.05(1H,s); 4.1(5H,m); 3.35(5H,m) ppm.

EXAMPLE 25

Preparation of (2S,4S)-2-[bis(S-pivaloyl-2-thioethyl) phosphono]-4-cytosin-1'-yl-1.3-dioxolane



Procedure: Dry BCH 4556 (dimethylaminomethylene derivative, 0.095 g, 0.354 mmol) was mixed with bis-(S-pivaloyl-2-thioethyl)-N,N-diisipropylphosphoramidite

(0.18 g, 0.5 mmol, prepared following the procedure described in P.R.No.27-25) and dissolved in dry dichloromethane (15 ml). ^{1}H-tetrazole (0.075 g, 1.06 mmol) was added and the combined solution was stirred under nitrogen atmosphere at room temperature for 1 hour. It was cooled to $-40^{0}C$ and treated with tert-butylhydroproxide (3 M solution in 2,2,4-trimethylpentane, 0.25 ml). Reaction mixture was allowed to warm up to room temperature during overnight. Solvent was evaporated and the residue was purified on a silica gel column using a mixture of ethyl acetate and methanol (ratio 40:1). Tare of the title product 0.055 g.

^{1}H NMR(400 MHz, $CDCl_3$) δ: 7.8(1H, d); 6.3(1H, t); 5.95(1H, d); 4.18(8H, m); 3.15(4H, m); 1.2(18H, s) ppm.

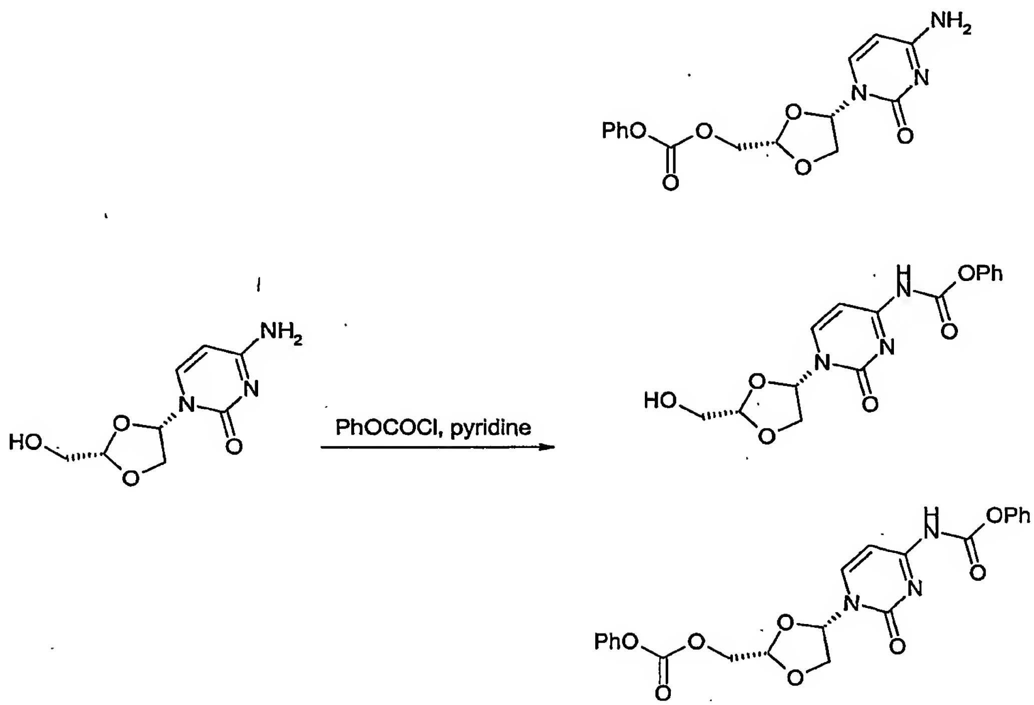
^{31}P NMR(16 MHz, $CDCl_3$) δ: -0.13

UV : λ_{max} (MeCN) 271nm

MS : m/e 582.4

EXAMPLE 26

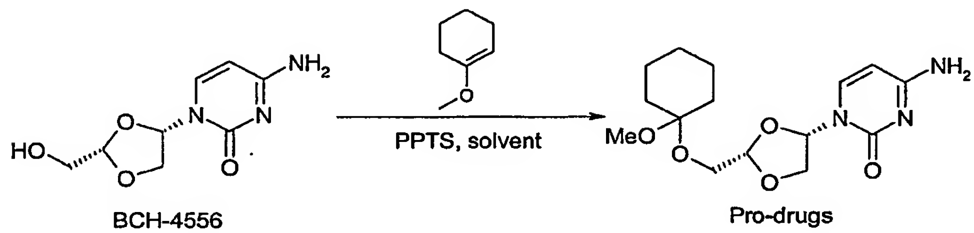
Typical procedure for the reaction with alkyl(or aryl) chloroformate

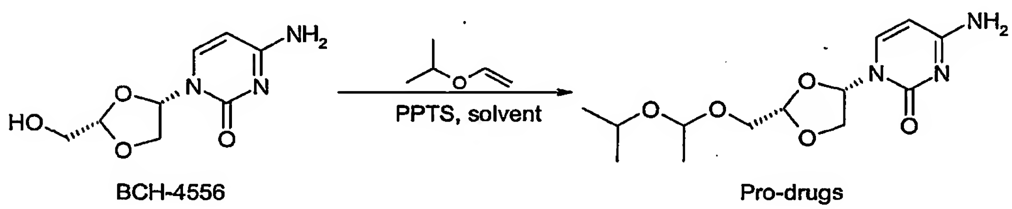


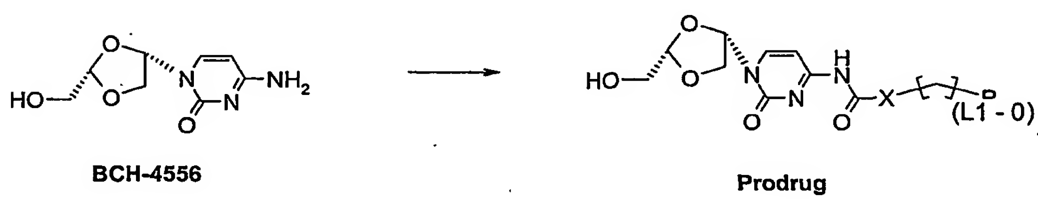
BCH-4556 (1 mmole) and phenyl chloroformate (1 mmole) were stirred for 24 hours in 10 mL of pyridine. Pyridine was then evaporated, the residue was dissolved in 10 mL of water and extracted with dichloromethane. The organic phase is dried on sodium sulfate evaporated and the residue is chromatographed on silica gel eliuuting firdt with 50/50 ethyl acetate/hexane, then ethyl acetate and finally with 10% MeOH/dichloromethane. The three compounds were isolated separately. The final products can be further purified using reverse phase preparative HPLC.

EXAMPLE 27

The following are additional synthesis reaction schemes.





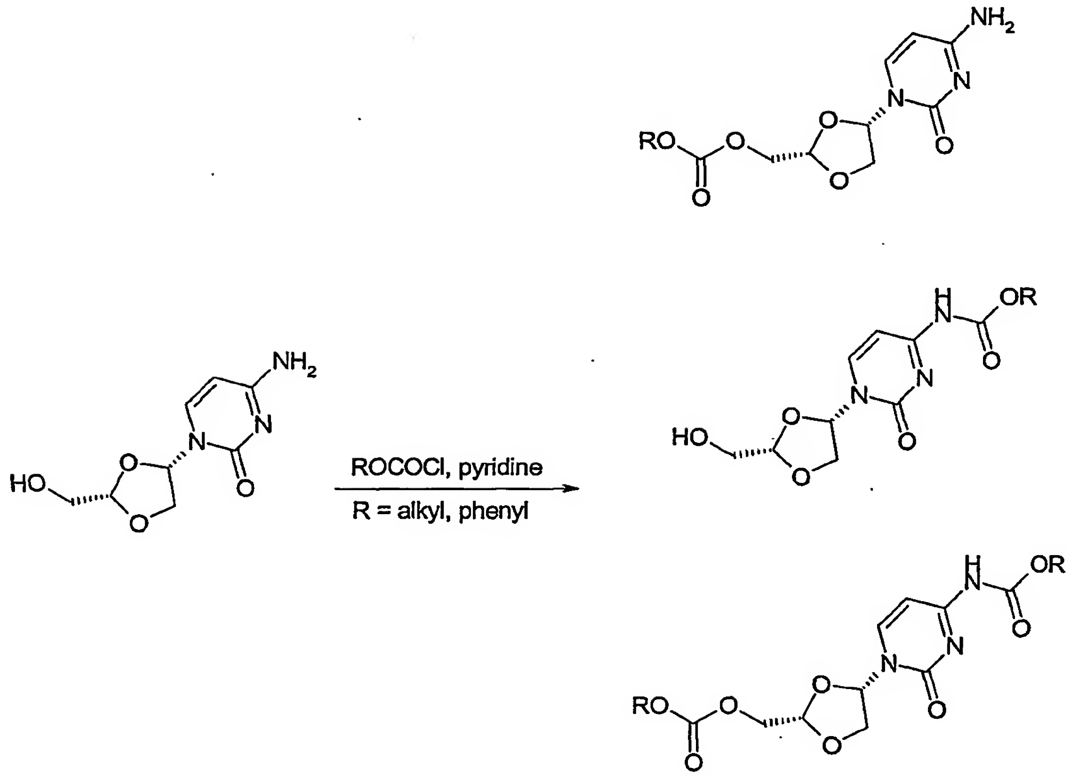


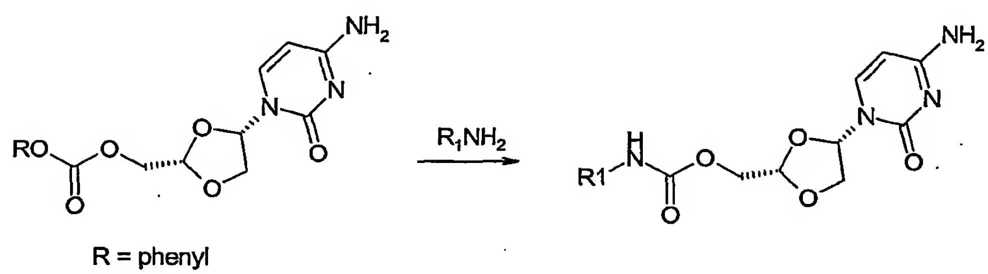
n = 3, 4, 5; X = CH_2; R = CH_3

n = 3, 4, 5; X = O; R = CH_3

n = 3, 4, 5; X = CH_2; R = $N(CH_3)_2$

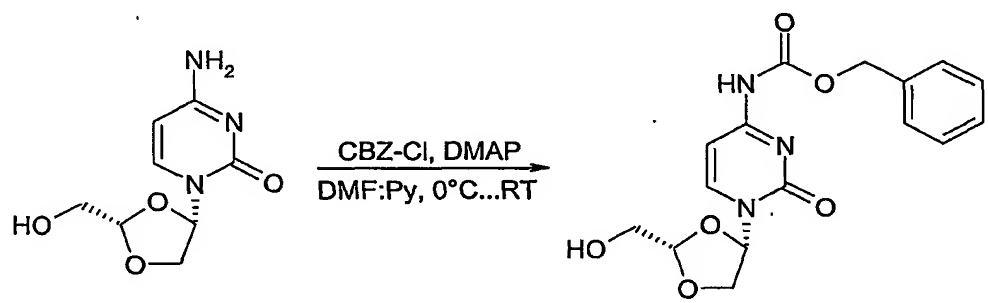
n = 3, 4, 5; X = O; R = $N(CH_3)_2$


NH2
N
N
O
HO
O
O
ROCOCl, pyridine
R = alkyl, phenyl
RO
O
OR


NH2
N
N
RO
O
R1NH2
R1
H
N
R = phenyl

EXAMPLE 28

Preparation of [1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)cysosyl]carbamic acid benzyl ester [BCH 19041]



(50)

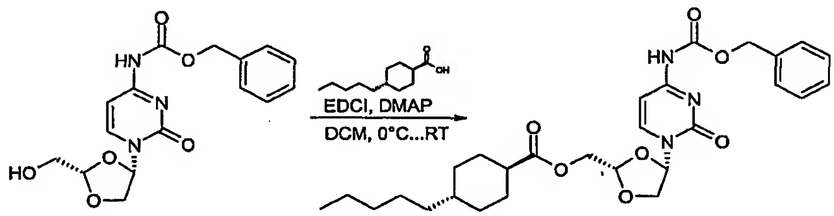
Procedure:

Benzylchloroformate (0.80 mL, 5.6 mmol) was added dropwise to a 0°C solution of BCH-4556 (955 mg, 4.48 mmol) and DMAP (657 mg, 5.38 mmol) in dimethylformamide and pyridine and stirred at room temperature for 18h. The reaction mixture was concentrated in vacuo. The oil obtained was partitionned between water (20mL) and dichloromethane (30mL). Aqueous layer was extracted with DCM. Organic layers were combined, dried over $MgSO_4$, filtered and concentrated to a yellow gum. The crude residue was purified by silaca gel biotage (40S) (100 % DCM to 10 % MeOH: 90 % DCM) to give 837 mg (54 % yield) of [1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)cysosyl]carbamic acid benzyl ester as a white powder, M.F. $C_{16}H_{17}N_3O_6$, M.W. 347.33.

^1H NMR (400 MHz, $CDCl_3$), δ ppm: 8.44 (d, 1H, J = 7.4Hz), 7.39-7.37 (m, 5H), 7.25 (m, 1H), 6.18 (d, 1H, J = 3.9Hz), 5.21 (s, 2H), 5.13-5.12 (m, 1H), 4.34 (d, 1H, J = 10.1Hz), 4.25 (dd, 1H, J = 5.2, 10.1Hz), 4.01-3.97 (m, 2H). MS: ES^+ 348.4 (M+1), ES^- 346.3 (M-1).

EXAMPLE 29

Preparation of [1{2-(trans-4-pentylcyclohexylcarboxy) oxy-methyl-[1,3]dioxolan-4-yl}cysosyl]carbamic acid benzyl ester



Procedure:

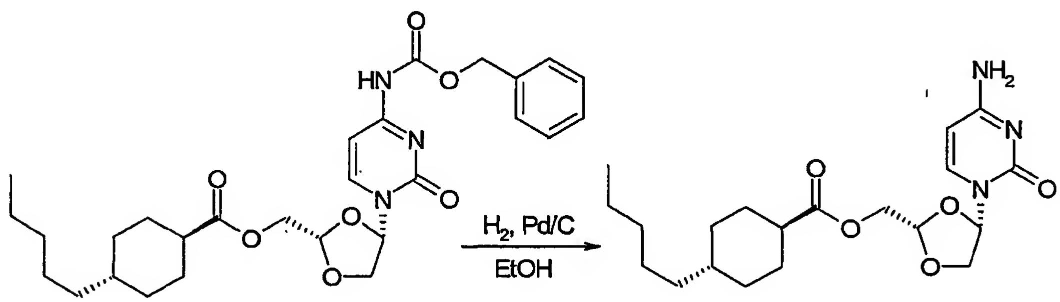
EDCI (1.66g, 8.64 mmol) was added to a 0°C solution of [1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)cysosyl]carbamic acid benzyl ester (2.5 g, 7.20 mmol), DMAP (1.05 g, 8.64 mmol) and trans-4-pentylcyclohexylcarboxylic acid (1.71g, 8.64 mmol) in dichloromethane and stirred at room temperature for 18h. The reaction was washed with HCl, saturated $NaHCO_3$ and brine. Organic layer was separated, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by silaca gel biotage (40M) (100 % DCM to 3 % MeOH: 97 % DCM) to give 3.92 g (100 % yield) of [1{2-(trans-4-pentylcyclohexylcarboxy) oxymethyl-[1,3]dioxolan-4-yl}cysosyl]carbamic acid benzyl ester as a white powder, M.F. $C_{28}H_{37}N_3O_7$, M.W. 527.62.

^1H NMR (400 MHz, $CDCl_3$), δ ppm: 8.15 (d, 1H, J = 7.4Hz), 7.39-7.31 (m, 5H), 7.30 (d, 1H, J = 7.4Hz), 6.19 (d, 1H, J = 4.1Hz), 5.24-5.22 (m, 3H), 4.55 (dd, 1H, J = 3.3, 12.7Hz), 4.32-4.22 (m, 3H), 2.31-2.23 (m,

1H), 1.99-1.91 (m, 2H), 1.85-1.80 (m, 2H), 1.49-1.37 (m, 1H), 1.31-1.16 (m, 10H), 0.98-0.86 (m, 5H).

EXAMPLE 30

Preparation of *trans*-4-Pentylcyclohexylcarboxylic acid 4-cytosyl-[1,3]dioxolan-2-ylmethyl ester



Procedure:

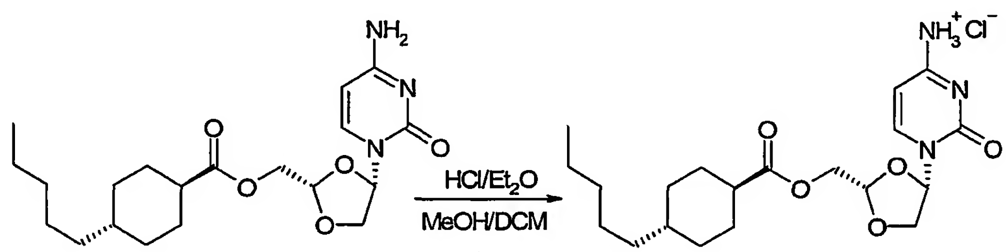
[1{2-(trans-4-pentylcyclohexylcarboxy)oxymethyl-[1,3]dioxolan-4-yl}cysosyl]carbamic acid benzyl ester (3.8g, 7.20 mmol) and Pd/C 10% (600 mg) were suspended in ethanol and EtOAc. The reaction was treated three times with a vacuum-nitrogen sequence and left under nitrogen. It was then submitted to a vacuum-hydrogen sequence and the reaction stirred under hydrogen for 3hrs. The reaction was filtered on a celite pad and washed with EtOH and the solution concentrated in vacuo. The crude solid was purified by silaca gel biotage (40M) to give 2.44 g (86 % yield) of trans-4-pentylcyclohexylcarboxylic acid 4-cytosyl-

[1,3]dioxolan-2-ylmethyl ester as a white powder, M.F. $C_{20}H_{31}N_3O_5$, M.W. 393.49.

^1H NMR (400 MHz, CD_3OD), δ ppm: 7.85 (d, 1H, J = 7.5Hz), 6.23 (dd, 1H, J = 1.9, 5.3Hz), 5.90 (d, 1H, J = 7.5Hz), 5.21 (t, 1H, J = 2.7Hz), 4.43 (dd, 1H, J = 2.7, 12.7Hz), 4.29 (dd, 1H, J = 2.6, 12.7Hz), 4.25-4.17 (m, 2H), 2.29-2.22 (m, 1H), 1.95-1.89 (m, 2H), 1.83-1.80 (m, 2H), 1.44-1.19 (m, 11H), 0.99-0.88 (m, 5H).

EXAMPLE 31

Preparation of *trans*-4-Pentylcyclohexylcarboxylic acid 4-cytosyl-[1,3]dioxolan-2-ylmethyl ester hydrochloride



salt

(264)

Procedure:

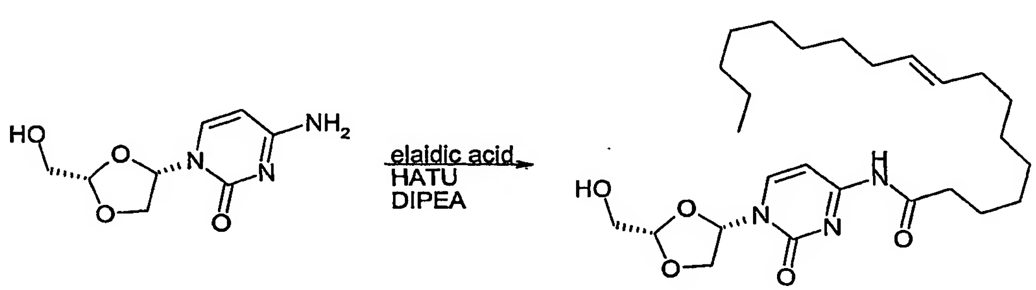
A 1M ether solution of HCl was added to a 0°C solution of trans-4-pentylcyclohexylcarboxylic acid 4-cytosyl-[1,3]dioxolan-2-ylmethyl ester in a 1:1 mixture of MeOH and DCM and the reaction strirred at

room temperature for 1.5h. Solvent was then removed in vacuo to give 99% yield of trans-4-pentylcyclohexylcarboxylic acid 4-cytosyl-[1,3]dioxolan-2-ylmethyl ester hydrochloride salt as a white powder, M.F. $C_{20}H_{31}N_3O_5$ HCl, M.W. 429.95.

^1H NMR (400 MHz, CD_3OD), δ ppm: 8.13 (d, 1H, J = 7.8Hz), 6.26 (dd, 1H, J = 1.5, 5.5Hz), 6.11 (d, 1H, J = 7.8Hz), 5.24 (t, 1H, J = 2.8Hz), 4.47 (dd, 1H, J = 2.8, 12.6Hz), 4.40 (dd, 1H, J = 1.2, 10.3), 4.31 (dd, 1H, J = 2.8, 12.6Hz), 4.22 (dd, 1H, J = 5.5, 10.3Hz), 2.31-2.25 (s, 1H), 1.96-1.91 (m, 2H), 1.85-1.82 (m, 2H), 1.42-1.19 (m, 11H), 0.96-0.88 (m, 5H).

EXAMPLE 32

Preparation of Octadecen-9-enoic[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



(216)

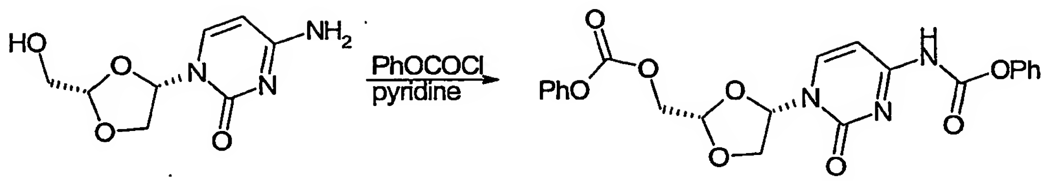
Procedure:

The starting material (BCH-4556, 86,3 mg, 0,405 mmole) is dissolved in DMF. Diisopropylethyl amine is then added (0,486 mmole, 1,2 eq) followed by the acid (0,521 mmole, 1,3 eq.). CH_2Cl_2 is then added to put everything in solution. HATU (168 mg, 0,446 mmole, 1,1 eq) is then added and the solution is stirred for 2 days. A saturated aqueous solution of $NaHCO_3$ is then added and extracted with CH2Cl2. The organic phase is evaporated and the residue is purified by Biotage with a Flash 12S column using 2% MeOH in CH_2Cl_2 followed by 4% MeOH in CH_2Cl_2. The desired fractions are recovered and evaporated to afford 39% of the desired compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8,98 (s, 1H), 8,46 (d, 1H, J=7,6 Hz), 7,42 (d, 1H, J=7,6 Hz), 6,18 (dd, 1H, J=5,2 and 1,4 Hz), 5,36 (m, 2H), 5,11 (t, 1H, J=1,8 Hz), 4,31 (dd, 1H, J=10,2 and 1,3 Hz), 4,23 (m, 1H), 3,86 (s, 2H), 3,02 (s, 1H), 2,44 (t, 2H, J=7,6 Hz), 1,94 (m, 4H), 1,64 (m, 2H), 1,43 (m, 20H), 0,86 (t, 3H, J=6,9 Hz).

EXAMPLE 33

Preparation of Carbonic acid 4-(2-oxo-4-phenoxycarbonylamino-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester phenyl ester



(43)

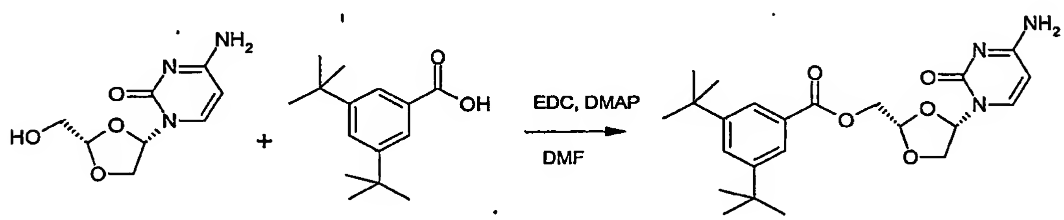
Procedure:

The starting material (BCH-4556, 105 mg, 0,493 mmole) is dissolved in 2 mL of pyridine and cooled to 0 °C. Phenyl chloroformate (68 µL, 0,542 mmole, 1,1 eq.) is added and the reaction mixture is warmed to room temperature and stirred overnight. The solvent is then evaporated and water is added. The aqueous phase is extracted with methylene chloride. The organic extracts are dried over Na_2SO_4 and evaporated. The residue is purified by Biotage with 50/50 AcOEt/Hexane then AcOEt followed by 10% $MeOH/CH_2Cl_2$. The fractions containing the fastest eluting spots are evaporated and repurified with preparative HPLC (C18 Deltapak 30×300 mm, 15% to 70% CH_3CN in water).

^1H nmr (400 MHz, $CDCl_3$) δ 8,31 (d, 1H, J=7,6 Hz), 7,39 (m, 4H), 7,26 (m, 3H), 7,16 (m, 4H), 6,31 (d, 1H, J=4,4 Hz), 5,32 (t, 1H, J=2,3 Hz), 4,69 (dd, 1H, J=12,6 and 2,6 Hz), 4,52 (dd, 1H, J=12,6 and 2,0 Hz), 4,38 (d, 1H, J=10,2 Hz), 4,30 (m, 1H).

EXAMPLE 34

3,5-Di-tert.-butyl-benzoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



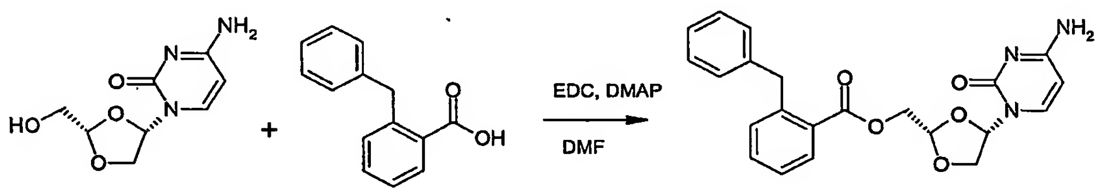
(186)

Procedure: The nucleoside (495 mg, 2.32 mmol, 1.0eq), 3,5-di-tButylbenzoic acid (545 mg, 2.32 mmol, 1.0eq), DMAP (30 mg, 0.23 mmol, 0.1eq) and EDC (445 mg, 2.32 mmol, 1.0eq) were mixed in DMF and stirred at room temperature. The solvent was mostly evaporated and the crude diluted in dichloromethane. The organic layer was washed twice with water, brine, dried over magnesium sulfate, filtered and evaporated to dryness. The desired compound was isolated by flash chromatography using a gradient of 3%-10% methanol in dichloromethane. 281 mg was obtained.

^{1}H NMR (400MHz, DMSO-d6): 7.76 (s, 2H), 7.70 (s, 1H), 7.49 (d, J=7.5Hz, 1H), 7.18 (br d, J=24.2Hz, 2H), 6.23 (m, 1H), 5.46 (d, J=7.5Hz, 1H), 5.26 (t, J=3.3Hz, 1H), 4.55 (m, 2H), 4.15-4.05 (m, 2H), 1.28 (m, 18H).

EXAMPLE 35

Preparation of 2-Benzyl-benzoic acid 4-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



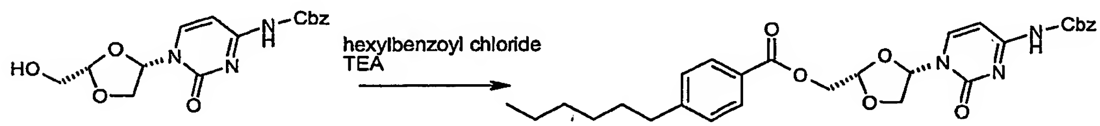
(220)

Procedure: The nucleoside (444 mg, 2.10 mmol, 1.0eq), alphaphenyl-o-toluic acid (445 mg, 2.10 mmol, 1.0eq), DMAP (27 mg, 0.21 mmol, 0.1eq) and EDC (400 mg, 2.10 mmol, 1.0eq) were mixed in DMF and stirred at room temperature. The solvent was mostly evaporated and the crude diluted in dichloromethane. The organic layer was washed twice with water, brine, dried over magnesium sulfate, filtered and evaporated to dryness. The desired compound was isolated by flash chromatography using a gradient of 3%-10% methanol in dichloromethane.

^{1}H NMR (400MHz, DMSO-d6): 7.77 (m, 1H), 7.56-7.48 (m, 2H), 7.38-7.31 (m, 2H), 7.24-7.08 (m, 7H), 6.23 (m, 1H), 5.44 (d, J=7.5Hz, 1H), 5.19 (t, J=3.0Hz, 1H), 4.47 (m, 2H), 4.27 (m, 2H), 4.11 (m, 2H).

EXAMPLE 36

Preparation Of 4-HEXYL-BENZOIC ACID 4-(4-METHYLAMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER



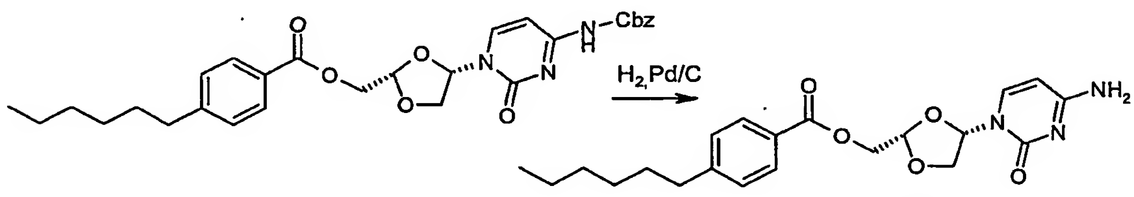
Procedure :

Acid chloride (64□L, 0.29mmol, 1eq.) was added to the mixture of the Cbz-protected BCH-4556 (101mg, 0.29mmol) in CH_2Cl_2 with TEA (0.12mL, 0.87mmol, 3eq.). Reaction mixture was stirred at room temperature for 2 days. Solvent was evaporated. Purification was done by flash chromatography using $MeOH/CH_2Cl_2$ 5% to give the desired compound plus some impurities.

^1H NMR (400MHz; $CDCl_3$): 8.12 (d, 1H, J=7.6Hz); 7.96-7.93 (m, 2H); 7.39-7.34 (m, 5H); 7.30-7.25 (m, 3H); 6.22 (dd, 1H; J=4.8 and 1.8Hz); 5.34 (t, 1H, J=3Hz); 5.21 (s, 2H); 4.77 (dd, 1H, J=3 and 12.7Hz); 4.58 (dd, 1H, J=3 and 12.7Hz); 4.32-4.24 (m, 2H); 2.69-2.65 (m, 2H); 1.66-1.60 (m, 2H); 1.35-1.27 (m, 6H); 0.88-0.85(m, 3H)ppm

EXAMPLE 37

Preparation of 4-HEXYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER



(191)

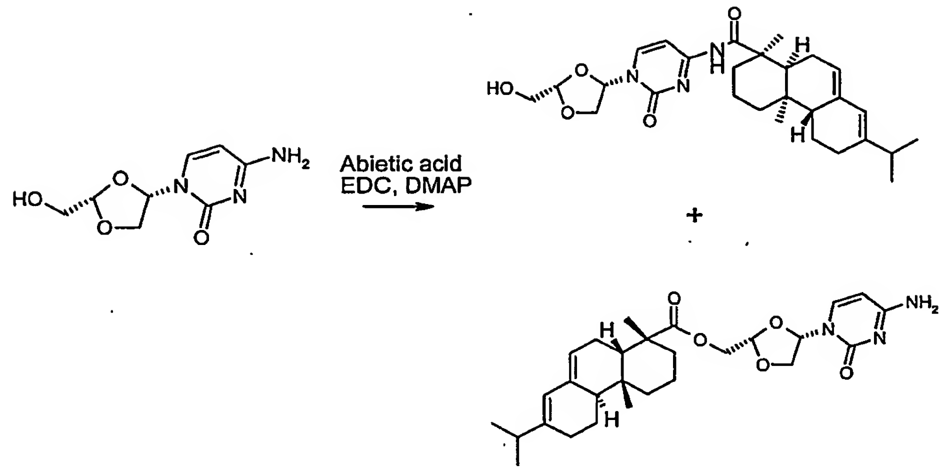
Procedure :

The protected compound (194mg, 0.29mmol) was dissolved in ethanol at 50°C, then purged with nitrogen. Pd/C was added, then the solution was put under H_2 atmosphere and stirred at 50°C. The solution was filtered and concentrated to give a foamy white solid. Purification by flash chromatography using $MeOH/CH_2Cl_2$ 3%.

^{1}H NMR (400MHz; DMSO): 7.87 (d, 1H, J=8.2Hz); 7.60 (d, 1H, J=7.4Hz); 7.37 (d, 1H, J=8.2Hz); 6.27 (t, 1H, J=3.7Hz); 5.64 (d, 1H, J=7.5Hz); 4.68-4.53 (m, 2H); 4.15 (d, 2H, J=3.9Hz); 2.67 (t, 2H, J=7.5Hz); 1.61-1.58 (m, 2H); 1.28 (m,6H) and 0.87-0.84 (m, 3H).ppm.

EXAMPLE 38

PREPARATION OF 7-ISOPROPYL-2,4A-DIMETHYL-1,2,3,4,4A,4B,5,6,10,10A-DECAHYDRO-PHENANTHRENE-2-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE or ESTER



Procedure :

EDC (90mg, 0.47mmol) was added to a solution of the acid (143mg, 0.47mmol) and the alcohol (101mg, 0.47mmol) in DMF followed by the addition of DMAP(6mg, 0.047mmol, 0.1eq.). Reaction mixture was stirred at room temperature overnight. Reaction mixture was poured into brine, extracted with EtOAc, combined extracts were washed with $NaHCO_3$ sat. solution, dried and concentrated to give a yellow oil.

Purification by flash chromatography using MeOH/EtOAc 10% to give two compounds.

Compound 1: amide (207)

^{1}H NMR (400MHz; $CDCl_3$): 8.42 (d, 1H, J=7.4Hz); 8.20 (bs,NH); 7.42 (d, 1H, J=7.6HZ); 6.18 (dd, 1H, J=5.2 and 1.2Hz); 5.74 (s, 1H); 5.30 (bt, 1H); 5.12 (t, 1H, J=1.8Hz); 4.36-4.24 (m, 2H); 3.98(s, 2H); 2.63-

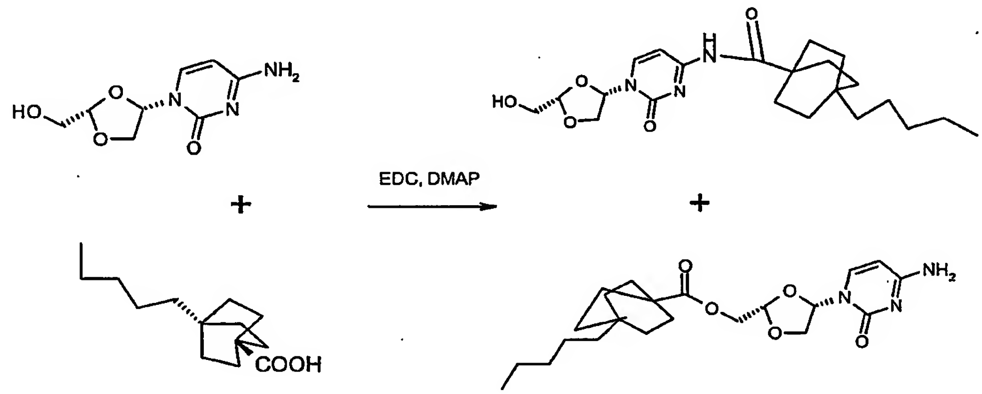
0.85(multiplets abietic part; similar to abietic acid) ppm

Compound 2: ester (281)

H NMR (400MHz; $CDCl_3$): 7.67 (d, 1H, J=7.5Hz); 6.19 (dd, 1H, J=2.8 and 4.5Hz); 5.71 (t, 1H, J=7.5Hz); 5.36 (d, 1H, J=3.1Hz); 5.18 (dd, 1H, J=2.1 and 4.7Hz); 4.48-4.09 (2m, 3H) and 2.24-0.83 (multiplets abietic part; similar to abietic acid) ppm

EXAMPLE 39

PREPARATION OF 4-PENTYL-BICYCLO[2.2.2]OCTANE-1-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE or ESTER



Procedure :

EDC (95mg, 0.50mmol) was added to a solution of the acid (112mg, 0.50mmol) and the alcohol (106mg, 0.50mmol) in DMF (0.5mL) followed by the addition of DMAP (6mg, 0.050mmol, 0.1eq.). Reaction mixture was stirred at room temperature overnight. Reaction mixture was poured into brine, extracted with EtOAc, combined extracts were washed with $NaHCO_3$ sat. solution, dried and concentrated to give a yellow oil.

Purification by flash chromatography using MeOH/EtOAc 10% to give two compounds.

Compound 1: amide (210)

^{1}H NMR (400MHz; $CDCl_3$): 8.34 (d, 1H, J=7.6Hz); 7.36 (d, 1H, J= 7.6Hz); 6.11 (dd, 1H, J=5.1 and 1.3Hz); 5.06 (t, 1H, J=1.8Hz); 4.28-4.16 (m, 2H); 3.91 (d, 1H, J=1.6Hz);

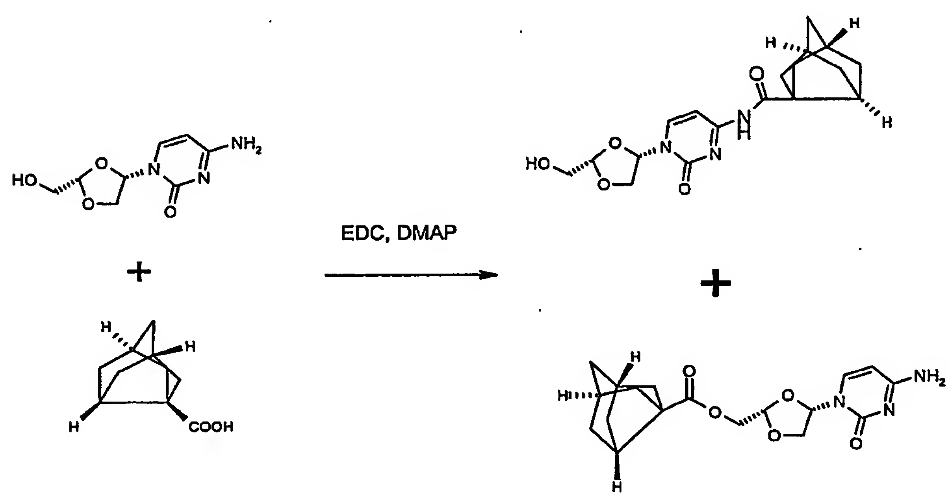
1.74-1.70 (m, 6H); 1.38-1.25 (m, 6H); 1.21 0.98(m, 8H); 0.81 (t, 3H, J=7.0Hz)ppm

Compound 2: ester (211)

H NMR (400MHz; $CDCl_3$): 7.64 (d, 1H, J=7.4Hz); 6.22 (dd, 1H, J= 2.8 and 4.3Hz); 5.77 (d, 1H, J=7.5Hz); 5.15 (t, 1H, J=3.5Hz); 4.41 (dd, 2H, J= 3.7 and 12.2Hz); 4.23-4.17 (m, 1H); 1.78-1.74 (m, 6H); 1.39-1.25 (m, 6H); 1.21 1.05(m, 8H); 0.86 (t, 3H, J=7.3Hz)ppm

EXAMPLE 40

HEXAHYDRO-2,5-METHANO-PENTALENE-3A-CARBOXYLIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE or ESTER



Procedure:

EDC (128mg, 0.67mmol) was added to a solution of the acid (111mg, 0.67mmol) and the alcohol (142mg, 0.67mmol) in DMF followed by the addition of DMAP (8mg, 0.067mmol, 0.1eq.). Reaction mixture was stirred at room temperature overnight. Reaction mixture was poured into brine, extracted with EtOAc, combined extracts were washed with $NaHCO_3$ sat. solution, dried and concentrated to give a yellow oil.

Purification by flash chromatography using MeOH/EtOAc 5% to give two compounds.

Compound 1: amide (231)

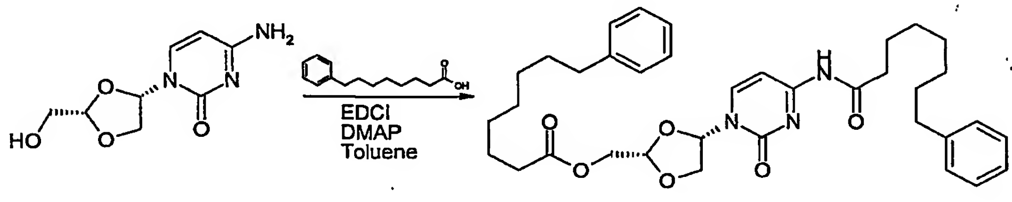
^{1}H NMR (400MHz; $CDCl_3$): 8.46 (d, 1H, J=7.5Hz); 7.98 (bs, 1H); 7.40 (d, 1H, J= 7.5Hz); 6.19 (d, 1H, J=4.9Hz); 5.12 (s, 1H); 4.33-4.21 (m, 2H); 3.98 (s, 2H); 3.28 (bs, 1H); 2.74 (t, 1H, J=6.7Hz); 2.37 (s, 1H); 2.16 (s, 2H); 2.04-2.01 (m, 2H); 1.86-1.82 (m, 4H) and 1.70-1.62 (m, 4H)ppm

Compound 2: ester (232)

H NMR (400MHz; $CDCl_3$): 7.74 (d, 1H, J=7.4Hz); 6.25 (t, 1H, J= 3.8Hz); 5.72 (d, 1H, J=7.4Hz); 5.23 (t, 1H, J=3.6Hz); 4.55-4.29 (m, 2H); 4.24 (d, 2H, J=3.7Hz); 2.72-2.71 (m, 1H); 2.33 (m, 2H); 2.11-2.08 (m, 2H); 1.85-1.82 (m, 4H) and 1.68-1.61 (m, 4H)ppm

EXAMPLE 41

Preparation of 8-Phenyl-octanoic acid 4-[2-oxo-4-(8-phenyl-octanoylamino)-2*H*-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester



(196)

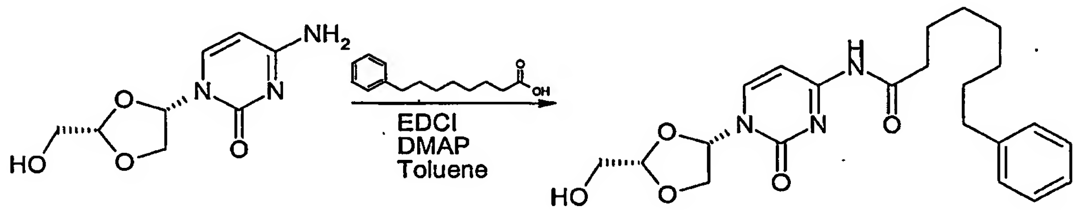
Procedure:

4-Amino-1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-1*H*-pyrimidin-2-one (0.23 mmol) was treated with 8-phenyl-octanoic acid (0.23 mmol), EDCI (0.35 mmol) and DMAP (catalytic amount) in DMF for 14 hours. The solution was neutralized with $NaHCO_3$ sat. and extracted with AcOEt. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by bond elute (2% $MeOH/CH_2Cl_2$ to 10% $MeOH/CH_2Cl_2$) to afford 8-Phenyl-octanoic acid 4-[2-oxo-4-(8-phenyl-octanoylamino)-2*H*-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester.

HNMR ($CDCl_3$) 8.70 (s, 1H), 8.15 (d, J= 7.5 Hz, 1H), 7.50 (d, J= 7.4 Hz, 1H), 7.30-7.17 (m, 10H), 6.22 (d, J= 4.7 Hz, 1H), 5.24 (t, J= 2.6 Hz, 1H), 4.58 (dd, J= 12.6, 2.8 Hz, 1H), 4.32-4.25 (m, 3H), 2.63-2.59 (m, 4H), 2.48-2.36 (m, 4H), 1.80-1.60 (m, 8H), 1.45-1.25 (m, 12H).

EXAMPLE 42

8-Phenyl-octanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide



(197)

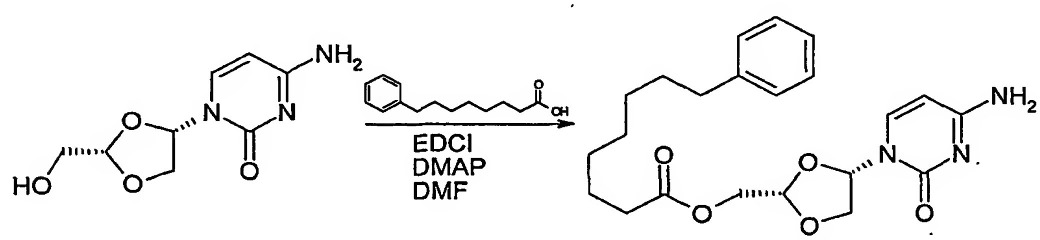
Procedure:

4-Amino-1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-1*H*-pyrimidin-2-one (0.23 mmol) was treated with 8-Phenyl-octanoic acid (0.23 mmol), EDCI (0.35 mmol) and DMAP (catalytic amount) in DMF for 14 hours. The solution was neutralized with $NaHCO_3$ sat. and extracted with AcOEt. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by bond elute (2% $MeOH/CH_2Cl_2$ to 10% $MeOH/CH_2Cl_2$) to produce 8-Phenyl-octanoic acid [1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-amide.

HNMR ($CDCl_3$) 8.62 (s, 1H), 8.49 (d, J= 7.5 Hz, 1H), 7.45 (d, J= 7.5 Hz, 1H), 7.30-7.27 (m, 2H), 7.20-7.17 (m, 3H), 6.20 (d, J= 4.5 Hz, 1H), 5.14 (s, 1H), 4.33-4.26 (m, 2H), 3.98 (s, 2H), 2.60 (t, J= 7.6 Hz, 2H), 2.45 (t, J= 7.5 Hz, 2H), 1.68-1.60 (m, 4H), 1.40-1.30 (m, 6H).

EXAMPLE 43

8-Phenyl-octanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



(198)

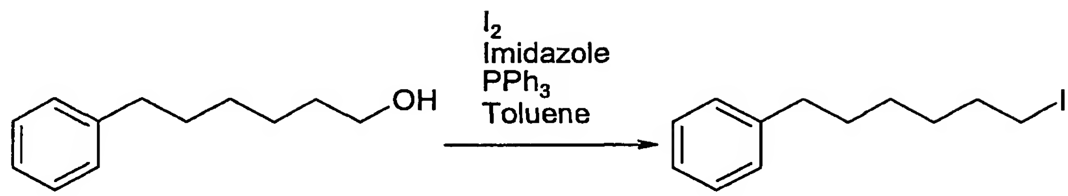
Procedure:

4-Amino-1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-1*H*-pyrimidin-2-one (0.23 mmol) was treated with 8-phenyl-octanoic acid (0.23 mmol), EDCI (0.35 mmol) and DMAP (catalytic amount) in DMF for 14 hours. The solution was neutralized with $NaHCO_3$ sat. (20 mL) and extracted with AcOEt. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by bond elute (2% $MeOH/CH_2Cl_2$ to 10% $MeOH/CH_2Cl_2$) to afford 0.015g (16%) of 8-phenyl-octanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester.

HNMR ($CDCl_3$) 9.4 (s, 1H), 7.71 (d, J= 7.5 Hz, 1H), 7.51-7.06 (m, 5H), 6.26 (dd, J= 5, 2 Hz, 1H), 5.78 (d, J= 7.5 Hz, 1H), 5.19 (t, J= 3.2 Hz, 1H), 4.48 (dd, J= 12.3, 3.3 Hz, 1H), 4.39-4.07 (m, 3H), 2.61 (t, J= 7.2 Hz, 2H), 2.36 (t, J= 7.4 Hz, 2H), 1.77-1.50 (m, 4H), 1.49-1.06 (m, 6H).

EXAMPLE 44

(6-Iodo-hexyl)-benzene



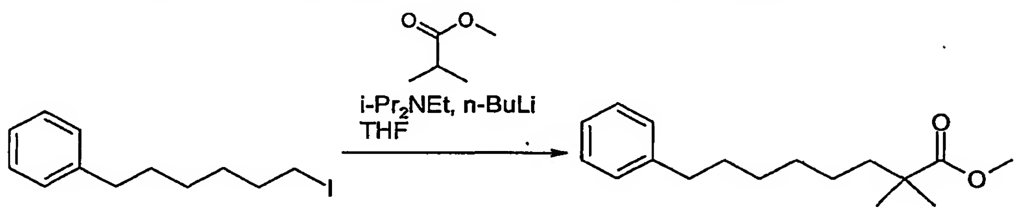
Procedure:

In a solution of 6-phenyl-hexan-1-ol (5.54 mmol) in toluene (0.2 M) was added in order PPh_3 (12.1 mmol), imidazole (24.9 mmol) and I_2 (11.6 mmol). The solution was mixed to reflux for 1.5 h and was cooled to room temperature. The solution was dissolved in Et_2O and washed with H_2O and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by biotage (100% pentane to 5% Et_2O/pentane) to produce (6-iodo-hexyl)-benzene.

HNMR ($CDCl_3$) 7.68-7.14 (m, 5H), 3.18 (t, J= 7 Hz, 2H), 2.61 (t, J= 7.6 Hz, 2H), 1.86-1.79 (m, 2H), 1.67-1.60 (m, 2H), 1.46-1.33 (m, 4H).

EXAMPLE 45

2,2-Dimethyl-8-phenyl-octanoic acid methyl ester



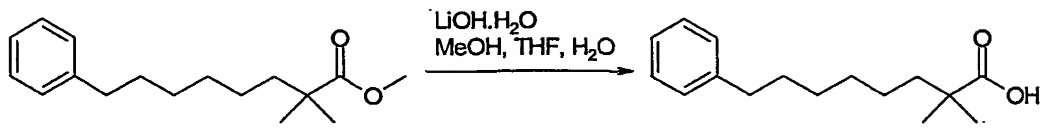
Procedure:

To a solution of i-Pr_2Net (2.12 mmol) in THF (0.2 M) was added a solution of 1.4 M *n*-BuLi in hexane (2.12 mmol) at 0°C. The mixture was stirred at 0°C for 30 minutes and cooled to -78°C for addition of isobutyric acid methyl ester (2.12 mmol). Then, the solution was stirred at -78°C for 1 hour and (6-Iodo-hexyl)-benzene (1.92 mmol) dissolved in THF was added slowly. This mixture was stirred 1 hour at -78°C and 3 hours at room temperature. The solution was dissolved in Et_2O and washed with NH_4Cl sat. and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by bond elute (3% Et2O/pentane) to afford 0.45g (90%) of 2,2-dimethyl-8-phenyl-octanoic acid methyl ester.

HNMR ($CDCl_3$) 7.29-7.25 (m, 2H), 7.18-7.15 (m, 3H), 3.64 (s, 3H), 3.48 (q, J= 7 Hz, 2H), 2.58 (t, J= 7.6 Hz, 2H), 1.59-1.47 (m, 2H), 1.32-1.25 (m, 2H), 1.20-1.14 (m, 10H).

EXAMPLE 46

2,2-Dimethyl-8-phenyl-octanoic acid



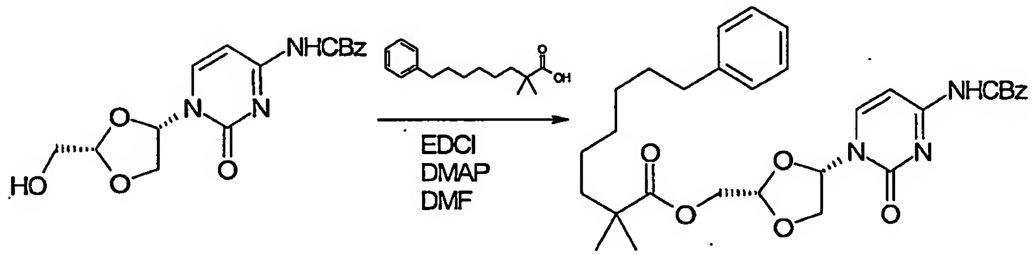
Procedure:

2,2-Dimethyl-8-phenyl-octanoic acid methyl ester (1.7 mmol) was dissolved in a MeOH, THF, H_2O solution (10:5:2). LiOH monohydrate was added and the solution was stirred and refluxed for 7 hours. The mixture was diluted with AcOEt and extracted with a solution of saturated $NaHCO_3$. The aqueous layers was combined, acidified with HCl 1 N and extracted with AcOEt. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum to afford 2,2-dimethyl-8-phenyl-octanoic acid.

HNMR ($CDCl_3$) 7.23-7.18 (m, 2H), 7.12-7.08 (m, 3H), 2.52 (t, J= 7.9 Hz, 2H), 1.55-1.43 (m, 4H), 1.26-1.18 (m, 6H), 1.11 (s, 6H).

EXAMPLE 47

2,2-Dimethyl-8-phenyl-octanoic acid 4-(4-benzyloxycarbonylamino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



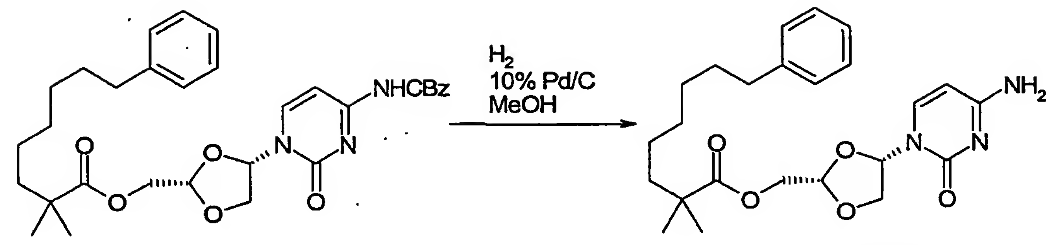
Procedure:

[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid benzyl ester (0.058 mmol) was treated with 2,2-dimethyl-8-phenyl-octanoic acid (0.058 mmol), EDCI (0.087 mmol) and DMAP (catalytic amount) in DMF. The solution was diluted in AcOEt and washed with $NaHCO_3$. sat. and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by bond elute (5% $MeOH/CH_2Cl_2$) to afford 2,2-Dimethyl-8-phenyl-octanoic acid 4-(4-benzyloxycarbonylamino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester.

HNMR (MeOD) 8.20 (d, J= 7.5 Hz, 1H), 7.44-7.34 (m, 5H), 7.27-7.10 (m, 7H), 6.19 (t, J= 3.6 Hz, 1H), 5.27 (t, J= 3.2 Hz, 1H), 5.23 (s, 2H), 4.70-4.47 (m, 2H), 4.31-4.23 (m, 2H), 2.62-2.54 (m, 2H), 1.63-1.49 (m, 4H), 1.39-1.15 (m, 12H).

EXAMPLE 48

2,2-Dimethyl-8-phenyl-octanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



(238)

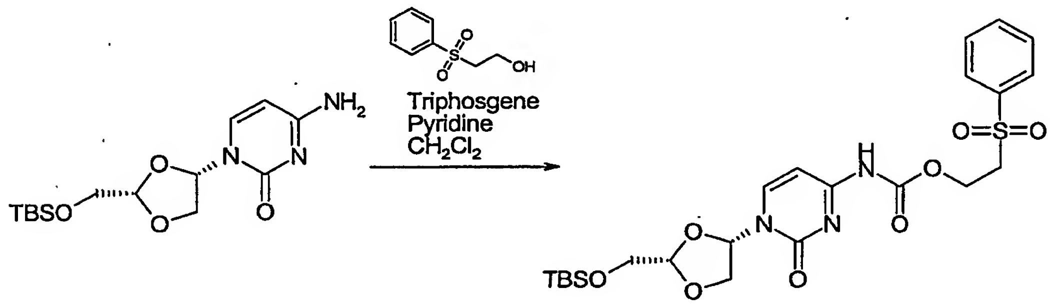
Procedure:

2,2-Dimethyl-8-phenyl-octanoic acid 4-(4-benzyloxycarbonylamino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester (0.048 mmol) was dissolved in MeOH. 10% Pd/C (30% w/w) was added and the solution was mixed under H_2 . The solution was filtered on celite and concentrated in vacuum. The residue was purified by bond elute (5% $MeOH/CH_2Cl_2$) to afford of 2,2-dimethyl-8-phenyl-octanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester.

HNMR (MeOD) 7.76 (d, J= 7.5 Hz, 1H), 7.24-7.20 (m, 2H), 7.14-7.11 (m, 3H), 6.20 (dd, J= 4.5, 2.9 Hz, 1H), 5.91 (d, J= 7.5 Hz, 1H), 5.18 (t, J= 3.4 Hz, 1H), 4.46 (dd, J= 12.4, 3.5 Hz, 1H), 4.24 (dd, J= 12.4, 3.2 Hz, 1H), 4.14 (t, J= 2.5 Hz, 2H), 2.56 (t, J= 7.6 Hz, 2H), 1.56-1.48 (m, 4H), 1.28-1.22 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H).

EXAMPLE 49

{1-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-[1,3]dioxolan-4-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 2-benzenesulfonyl-ethyl ester



Procedure:

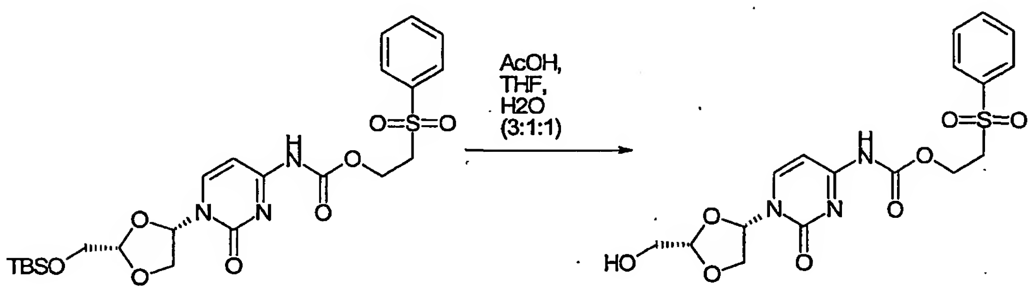
To a solution of triphosgene and 2-benzenesulfonyl-ethanol in CH_2Cl_2 was added pyridine at 0°C. This solution was mixed at 0°C added to a solution of 4-amino-1-[2-(*tert*-butyl-dimethyl-silanyloxymethyl)-[1,3]dioxolan-4-yl]-1*H*-pyrimidin-2-one and pyridine in CH_2Cl_2. The resulting solution was mixed and diluted in CH_2Cl_2. The mixture was washed with water and the organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by bond elute (3% MeOH/CH2Cl2) to afford {1-[2-(*tert*-butyl-dimethyl-silanyloxymethyl)-[1,3]dioxolan-4-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 2-benzenesulfonyl-ethyl ester.

HNMR ($CDCl_3$) 8.36 (d, J= 7.2 Hz, 1H), 7.84-7.80 (m, 2H), 7.62-7.45 (m, 4H), 6.98 (s, 1H), 6.10 (dd, J= 4.7, 1.9 Hz, 1H), 4.94 (t, J= 1.9 Hz, 1H), 4.43 (t, J= 5.4

Hz, 2H), 4.16-4.08 (m, 2H), 3.93-3.84 (m, 2H), 3.46-3.42 (m, 2H), 0.82 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

EXAMPLE 50

[1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 2-benzenesulfonyl-ethyl ester



(167)

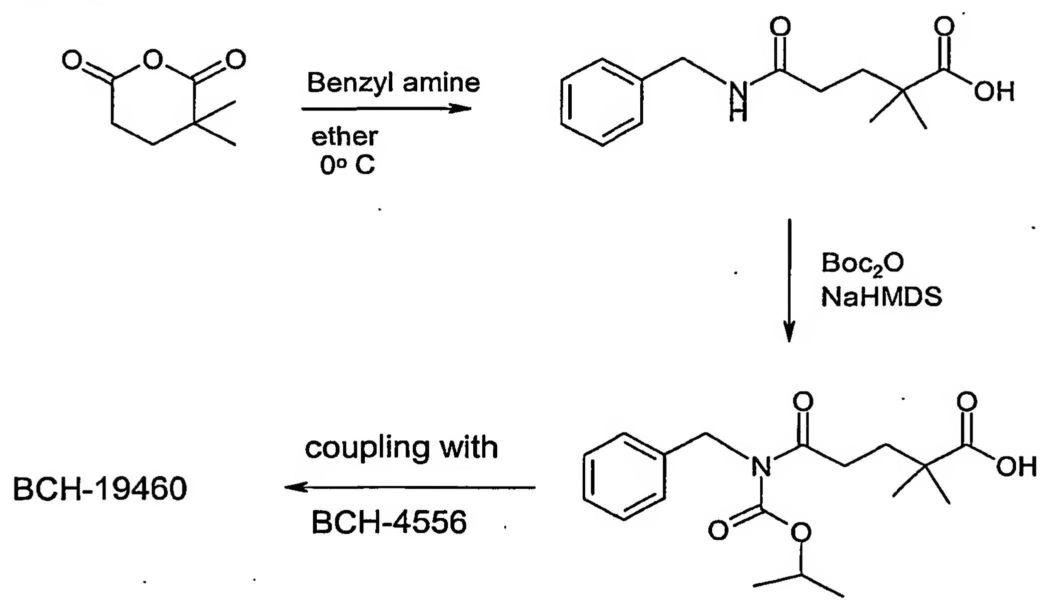
Procedure:

{1-[2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-[1,3]dioxolan-4-yl]-2-oxo-1,2-dihydro-pyrimidin-4-yl}-carbamic acid 2-benzenesulfonyl-ethyl ester (0.087mmol) was dissolved in a solution of AcOH, THF, H_2O (3:1:1) and was mixed. The mixture was dissolved in AcOEt and washed with H_2O, brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by bond elute (5% MeOH/CH_2Cl_2) to afford [1-(2-Hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid 2-benzenesulfonyl-ethyl ester.

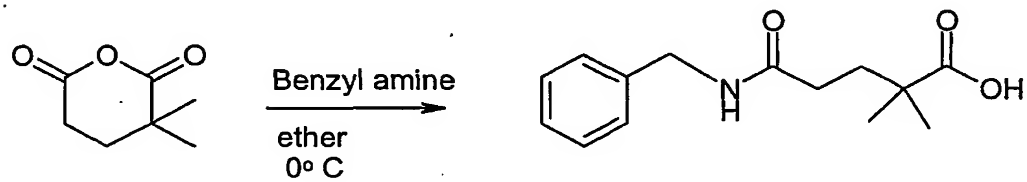
HNMR ($CDCl_3$) 8.45 (d, J= 7.5 Hz, 1H), 7.93-7.90 (m, 2H), 7.70-7.65 (m, 2H), 7.59-7.55 (m, 2H), 7.08 (s, 1H), 6.17 (dd, J= 5.1, 1.2 Hz, 1H), 5.12 (t, J= 1.6 Hz, 1H), 4.53 (d, J= 5.9 Hz, 2H), 4.33 (dd, J= 10.6, 1.3 Hz, 1H), 4.23 (dd, J= 10.2, 5.1 Hz, 1H), 3.97 (s, 2H), 3.54-3.51 (m, 2H), 2.6 (s, 1H).

EXAMPLE 51

5-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-5-oxo-pentanoic acid



A) **4-Benzylcarbamoyl-2,2-dimethyl-butyric acid**

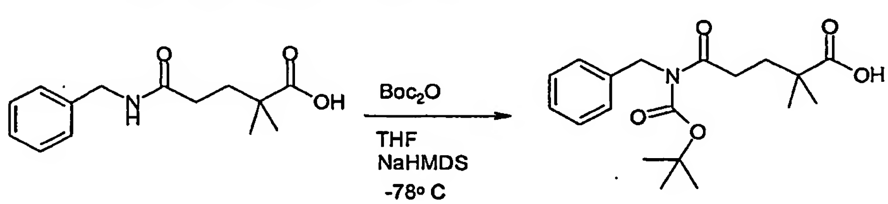


Procedure:

To a solution of 3,3-dimethyl-dihydro-pyran-2,6-dione (1.76 mmole) in diethyl ether at 0° C was added benzyl amine (1.76 mmole) dropwise. As soon as addition was made, solid started to separate. The mixture was stirred at 0° C for 15 minutes. It was diluted with ether. The solution was washed with 0.1 N HCl, and with saturated sodium chloride solution and dried over sodium sulfate. The crude product obtained after removing the solvent was passed through a bond-elute (eluents: CH_2Cl_2, 2 and 4 % MeOH in CH_2Cl_2) yielding 4-benzylcarbamoyl-2,2-dimethyl-butyric acid (57%).

HNMR (δ, CD_3OD) : 7.23-7.32 (5H, m), 4.34 (2H, s), 2.21-2.26 (2H, m), 1.83-1.87 (2H, m), 1.18 (6H, s).

B) **5-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-5-oxo-pentanoic acid**



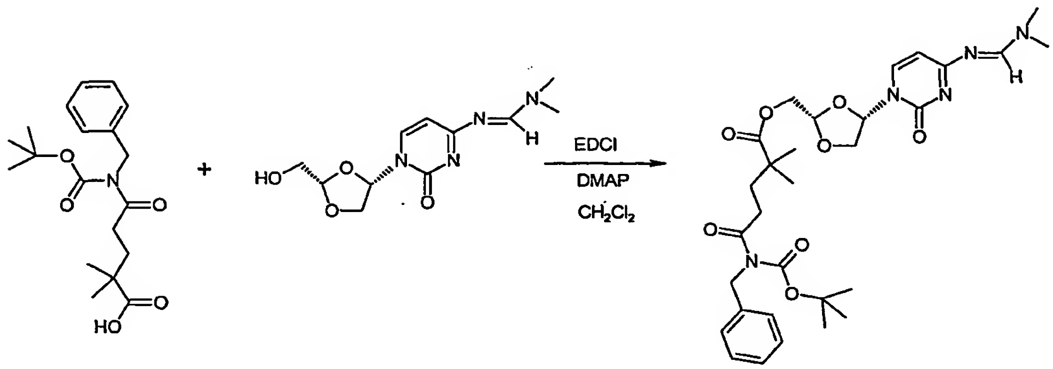
Procedure:

To a solution of 4-benzylcarbamoyl-2,2-dimethyl-butyric acid (0.09 mmole) in THF at -78° C was added NaHMDS in THF (1M) dropwise. It was stirred at -78° C for 15 minutes. Di-*tert*-butyl dicarbonate (0.1 mmole) in THF was added. It was stirred at this temperature for 15 minutes. Saturated NH_4Cl solution was added and the mixture was allowed to come to room temperature. It was acidified with dil. HCl and extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed and the residue was passed through a bond-elute (eluents : CH_2Cl_2 and 5% MeOH in CH_2Cl_2) yielding 5-(benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-5-oxo-pentanoic acid (39%).

HNMR (δ, $CDCl_3$) : 7.22-7.31 (5H, m), 4.87 (2H, s), 2.91-2.95 (2H, m), 1.93-1.97 (2H, m), 1.40 (9H, s), 1.24 (6H, s).

__EXAMPLE 52__

5-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-5-oxo-pentanoic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2*H*-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester



(166)

Procedure:

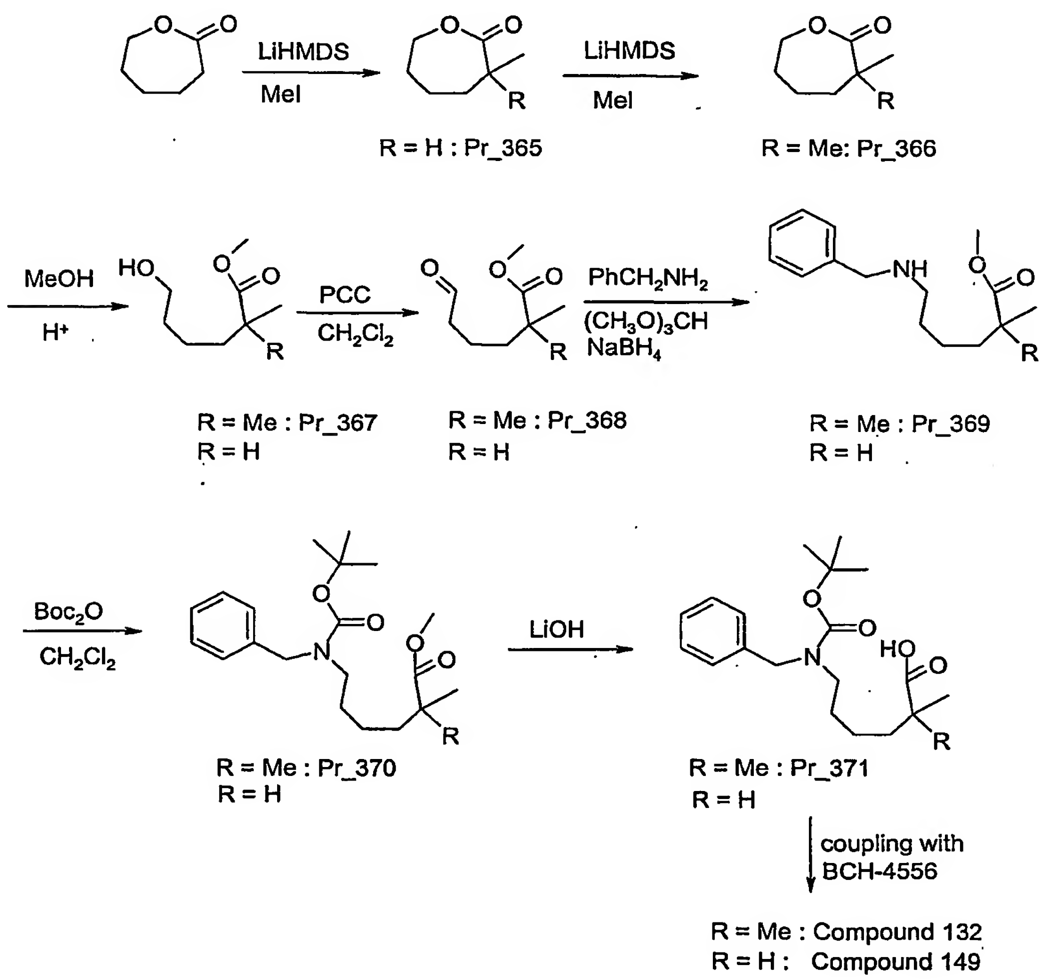
To a solution of N'-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-N,N-dimethyl-formamidine (0.034 mmole), 5-(benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-5-oxo-pentanoic acid (0.034 mmole) and DMAP in CH_2Cl_2 at 0° C was added EDCI (0.078 mmole) in CH_2Cl_2 dropwise. The mixture was stirred at 0° C for 0.5 hr and then at room temperature for 18 hrs. It was diluted with CH_2Cl_2, washed with water and saturated sodium chloride solution. The solution was dried over sodium sulfate and the solvent was evaporated. The pure ester was obtained after flash chromatography over bond-elute (eluents: CH_2Cl_2, 2 and 4 % MeOH in CH_2Cl_2) in 44% yield.

HNMR (δ, CD_3OD): 8.67 (1H, s), 7.97 (1H, d, J = 7.2 Hz), 7.16-7.30 (5H, m), 6.20 (1H, d, J = 7.2 Hz), 6.17 (1H, t, J = 3.7 Hz), 5.25 (1H, dd, J = 2.9, 3.4 Hz), 4.83 (2H, fine split signal), 4.57 (1H, dd, J = 3.5, 12.6 Hz), 4.27 (1H, dd, J = 2.9, 12.5 Hz), 4.21 (2H, d, J = 3.7 Hz), 3.21, 3.13 (3H each, fine split singlets),

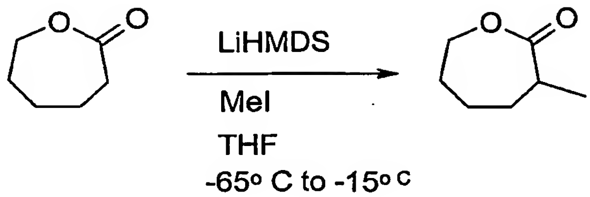
2.86-2.92 (2H, m), 1.89-1.93 (2H, m), 1.36 (9H, s), 1.24, 1.22 (3H each, s).

EXAMPLE 53

6-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid and 6-(benzyl-*tert*-butoxycarbonyl-amino)-2-methyl-hexanoic acid



A) 3-Methyl-oxepan-2-one

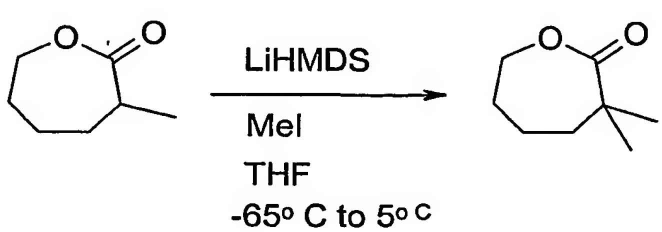


Procedure:

A solution of oxepan-2-one (4.54 mmole) in THF cooled to -65°C was treated with LiHMDS (1M). The mixture was stirred at -65°C. Methyl iodide (8.03 mmole) was added. The temperature was raised slowly to -15°C. Saturated NH_4Cl solution was added. The mixture was extracted with diethyl ether. The solution was dried over sodium sulfate and the solvent was evaporated. The crude was passed through a bond-elute (eluent: pentane-ether mixture - 1:1) yielding 3-methyl-oxepan-2-one contaminated with small amount of 3,3-dimethyl-oxepan-2-one (about 13% from NMR) (around 52 %).

HNMR (δ, $CDCl_3$): 4.20-4.34 (2H, m), 2.71-2.76 (1H, m), 1.93-2.01 (2H, m), 1.52-1.76 (4H, m), 1.23 (3H, d, J = 6.7 Hz)

A) 3,3-Dimethyl-oxepan-2-one

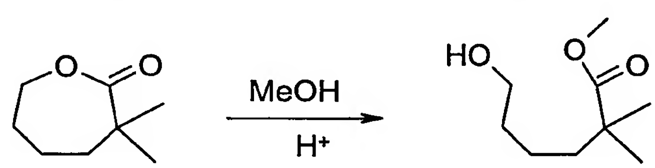


Procedure:

A solution of 3-methyl-oxepan-2-one (containing 13% of 3,3-dimethyl-oxepan-2-one) in THF at -65°C was treated with LiHMDS (1M) dropwise. The mixture was stirred at -65°C and methyl iodide (28.6 mmole) was added. The temperature was slowly raised to 5°C. It was stirred at 5°C and saturated NH_4Cl solution was added. The mixture was extracted with diethyl ether. The extracts were dried over sodium sulfate and the solvent was removed. The crude on passing through a bond-elute (eluent: pentane-ether-1:1) gave pure 3,3-dimethyl-oxepan-2-one (approx. 26%).

HNMR (δ, $CDCl_3$) : 4.24-4.27 (2H, m), 1.71-1.79 (4H, m), 1.55-1.58 (2H, m), 1.25 (6H, s).

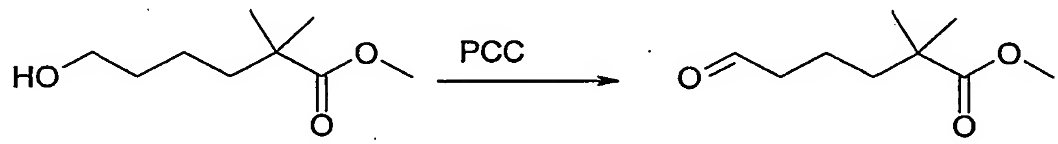
C) 6-Hydroxy-2,2-dimethyl-hexanoic acid methyl ester



Procedure:

Methanolic HCl was prepared by adding acetyl chloride to dry MeOH slowly. 3,3-Dimethyl-oxepan-2-one (0.7 mmole) was treated with this solution. The mixture was stirred at room temperature. The solvent was removed. The residue was dissolved in diethyl ether. The solution was washed with $NaHCO_3$ solution and saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed. The crude product was pure enough for the next step.

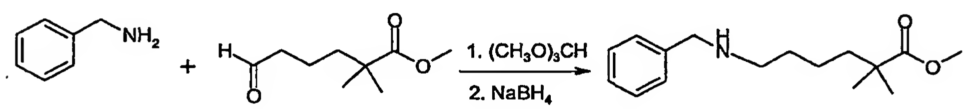
D) 2,2-Dimethyl-6-oxo-hexanoic acid methyl ester



Procedure:

A mixture of 6-hydroxy-2,2-dimethyl-hexanoic acid methyl ester, molecular sieves 4A° and PCC in CH_2Cl_2 was stirred at 0°C for 1 hr. It was diluted with diethyl ether and filtered through a bed of silica gel. The solvent was removed from the filtrate. The crude aldehyde thus obtained was pure enough for the next step.

E) 6-Benzylamino-2,2-dimethyl-hexanoic acid methyl ester



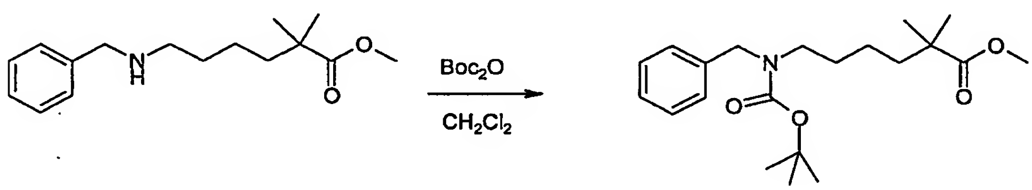
Procedure:

A mixture of benzyl amine (0.38 mmole) and methyl orthoformate (7.3 mmole) was stirred at room temperature for 5 minutes. This solution was added to crude 2,2-dimethyl-6-oxo-hexanoic acid methyl ester (0.33 mmole). It was stirred for 6 hrs. and evaporated to dryness. The residue was dissolved in MeOH and the solution was cooled to 0° C. Sodium borohydride was added in portions and the mixture was

stirred. MeOH was removed and the residue was taken up in ethyl acetate. The solution was washed with saturated sodium chloride solution, dried and evaporated. The crude was passed through a bond-elute (eluents: CH_2Cl_2, and 1 and 2% MeOH in CH_2Cl_2) yielding pure 6-benzylamino-2,2-dimethyl-hexanoic acid methyl ester (13% in three steps)

HNMR (δ, $CDCl_3$): 7.24-7.33 (5H, m), 3.78 (2H, s), 3.64 (3H, s), 2.61 (2H, t, J = 7.2 Hz), 1.45-1.53 (4H, m), 1.21-1.26 (2H, m), 1.15 (6H, s).

F) 6-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid methyl ester

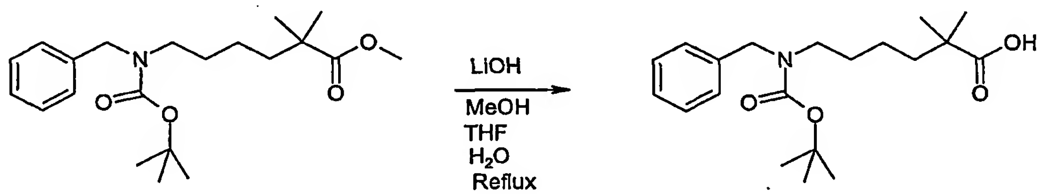


Procedure:

To a solution of 6-benzylamino-2,2-dimethyl-hexanoic acid methyl ester (0.09 mmole)in CH_2Cl_2 (3 ml) at 0° C was added di-*tert*-butyl dicarbonate (0.14 mmole) in CH_2Cl_2. The mixture was stirred at room temperature for 2 hrs. It was evaporated to dryness and passed through a bond-elute yielding pure 6-(benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid methyl ester (85%).

HNMR (δ, $CDCl_3$): 7.21-7.33 (5H, m), 4.39-4.42 (2H, two broad signals), 3.63 (3H, s), 3.10-3.19 (2H, broad signal), 1.43-1.48 (13H, two broad signals), 1.13 (8H, broad singlet).

G) 6-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid



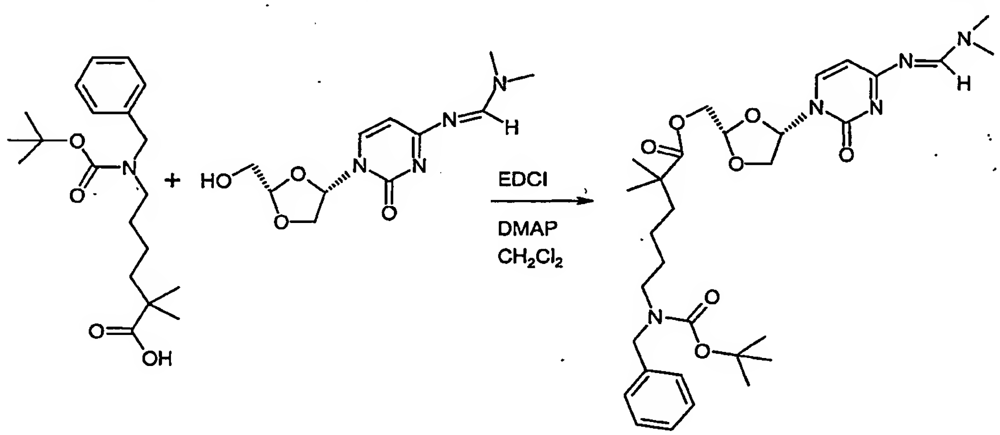
Procedure:

To a solution of 6-(benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid methyl ester (0.06 mmole) in THF and MeOH (2:1) was added $LiOH.H_2O$ (0.26 mmole) in H_2O. The mixture was refluxed for 7 hrs and stirred at room temperature for 16 hrs. It was evaporated to dryness. The residue was taken up in water and acidified with 0.1 N HCl. It was extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. The crude was passed through a bond-elute (eluents: CH_2Cl_2 and 5 % acetone in CH_2Cl_2) yielding pure 6-(benzyl-*tert*-butoxycarbonyl-amino)-hexanoic acid (12 mg; 57%).

HNMR (δ, $CDCl_3$): 7.22-7.33 (5H, m), 4.40-4.43 (2H, broad signal), 3.12-3.20 (2H, broad signal), 1.43-1.48 (13H, two broad signals), 1.21-1.25 (2H, m), 1.16 (6H, s).

EXAMPLE 54

6-(Benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2*H*-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester



(132)

Procedure:

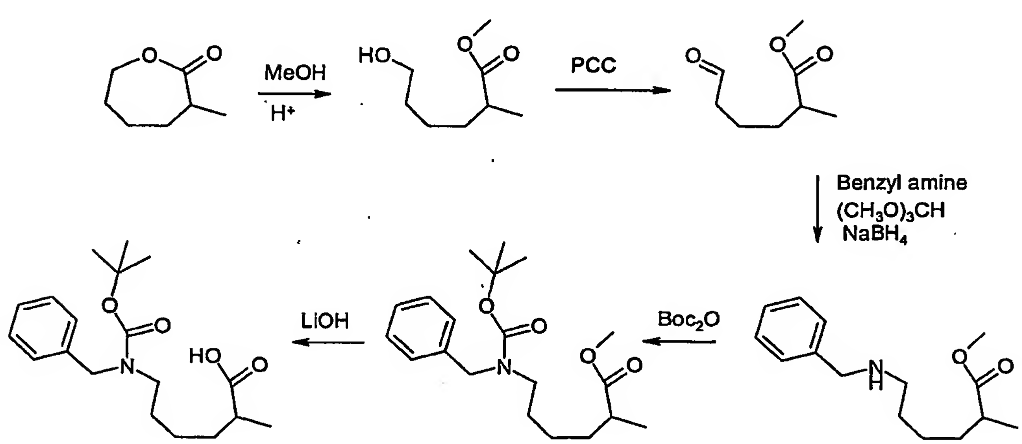
To a mixture of N'-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-N,N-dimethyl-formamidine (0.03 mmole), 6-(benzyl-*tert*-butoxycarbonyl-amino)-2,2-dimethyl-hexanoic acid (0.03 mmole) and DMAP (0.3 mg) in dichloromethane (0.3 ml) at 0 °C was added EDCI (0.063 mmole) in dichloromethane dropwise. It was stirred for 30 minutes at this temperature and at room temperature for 18 hrs. The mixture was diluted with dichloromethane, washed with water and saturated sodium chloride solution. The

solution was dried over sodium sulfate and evaporated. The crude product was passed through a bond-elute (eluents: dichloromethane, 1 and 2% MeOH in dichloromethane) yielding the ester (28 % yield)

HNMR(δ, CD_3OD) : 8.69 (1H, s), 7.96 (1H, d, J = 7.3 Hz), 7.19-7.32 (5H, m), 6.19-6.23 (2H, m), 5.23 (1H, t, J = 3.2 Hz), 4.49 (1H, dd, J = 3.4, 12.5 Hz), 4.39 (2H, s), 4.22-4.28 (3H, m), 3.22, 3.14 (3H each, s), 1.29-1.47 (15 H, three broad signals), 1.17, 1.16 (3H each, s).

EXAMPLE 55

6-(Benzyl-*tert*-butoxycarbonyl-amino)-2-methyl-hexanoic acid

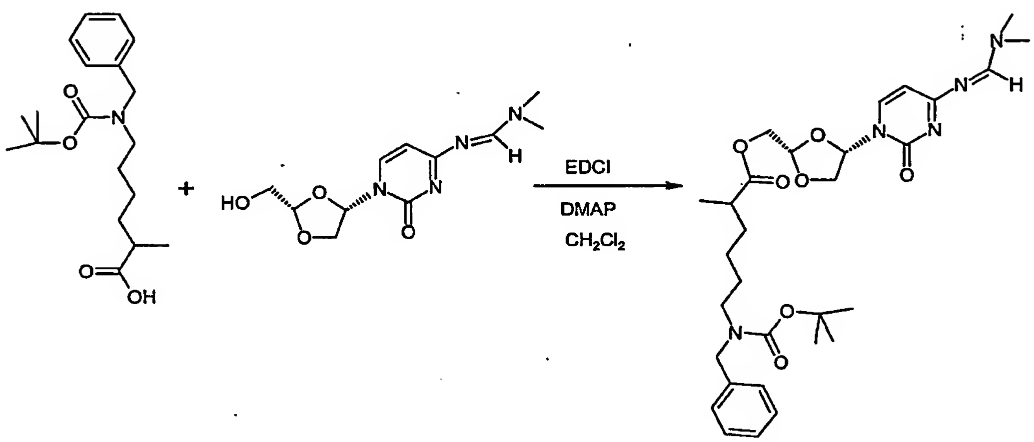


Procedure:

The procedure to obtain this compound is similar to procedures described in previous examples.

EXAMPLE 56

6-(Benzyl-*tert*-butoxycarbonyl-amino)-2-methyl-hexanoic acid 4-[4-(dimethylamino-methyleneamino)-2-oxo-2*H*-pyrimidin-1-yl]-[1,3]dioxolan-2-ylmethyl ester



(149)

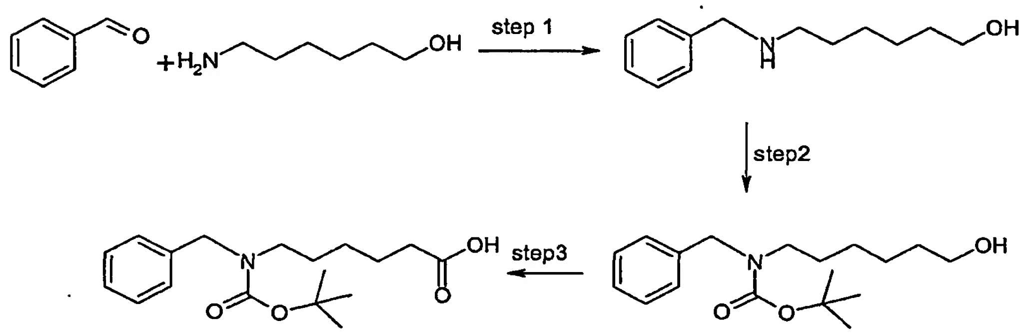
Procedure:

To a solution of N'-[1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-N,N-dimethyl-formamidine (0.036 mmole), 6-(benzyl-*tert*-butoxycarbonyl-amino)-2-methyl-hexanoic acid (0.036 mmole) and DMAP (0.4 mg) in dichloromethane at 0 °C was added EDCI (0.078 mmole) in dichloromethane dropwise. The mixture was stirred at 0 °C for 30 minutes and then at room temperature for 2.5 hrs. It was diluted with dichloromethane (50 ml), washed with water and saturated sodium chloride solution. The solution was dried over sodium sulfate and evaporated. The crude was passed through a bond-elute (eluents : CH_2Cl_2, 1 and 2 % MeOH in CH_2Cl_2) and the pure ester was obtained in 62% yield.

HNMR (δ, CD_3OD) : 8.68 (1H, s), 8.02 (1H, two doublets, J = 7.3 Hz), 7.20-7.32 (5H, multiplets), 6.17-6.25 (2H, m), 5.23-5.25 (1H, broad signal), 4.52 (1H, two dd, J = 2.4, 12.1 Hz), 4.39- 4.40 (total 2H, broad signals), 4.20-4.31 (3H, m), 3.21, 3.12 (3H each, s), 2.46 (1H, q, J = 7.0 Hz), 1.20-1.67 (15H, multiplets), 1.12, 1.11 (total 3H, two doublets, J = 7.0 Hz).

EXAMPLE 57

6-(Benzyl-*tert*-butoxycarbonyl-amino)-hexanoic acid

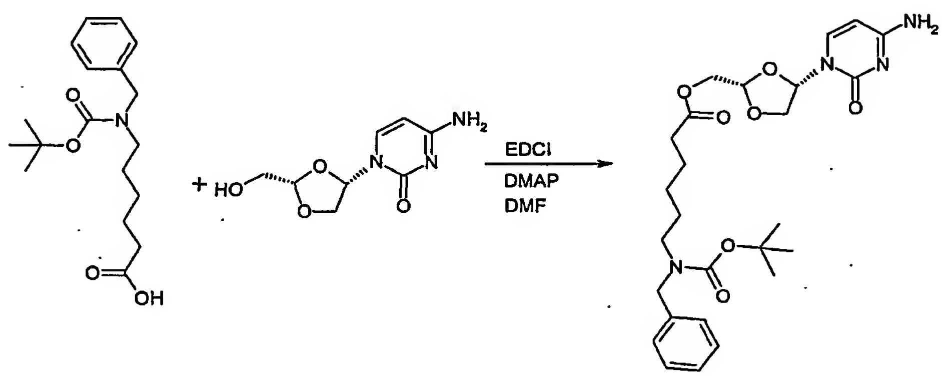


Procedure

Steps 1 and 2 were carried out as described in N. Mourier, M. Camplo, G. S. Della Bruna, F. Pellacini, D. Ungheri, J.-C. Chermann and J.-L. Kraus, **Nucleosides, Nucleotides & Nucleic Acids**, *19* (7), 1057-91 (2000), step 3 was substituted by a Jones oxidation as described in R. N. Rej, J. N. Glushka, W. Chew and A. S. Perlin, **Carbohydrate Research**, *189* (1989), 135-148.

EXAMPLE 58

6-(Benzyl-*tert*-butoxycarbonyl-amino)-hexanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



Procedure:

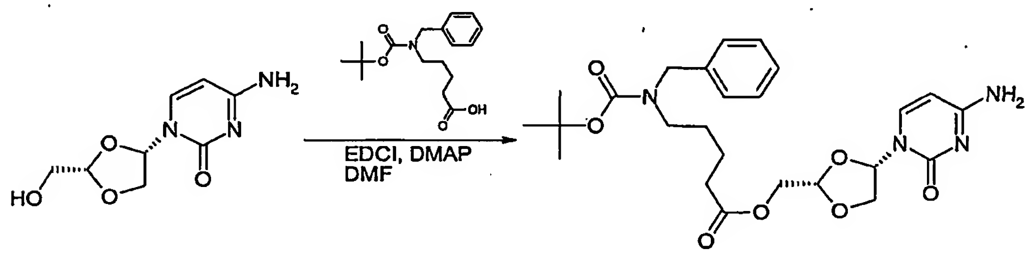
A mixture of 4-amino-1-(2-hydroxymethyl-[1,3]dioxolan-4-yl)-1*H*-pyrimidin-2-one (0.11 mmole), 6-(benzyl-*tert*-butoxycarbonyl-amino)-hexanoic acid (0.11 mmole), EDCI (0,156 mmole) and DMAP (3 mg) in DMF was stirred at room temperature for 16 hrs. DMF was removed in vacuum. The residue was taken up in ethyl acetate, washed with water and saturated sodium chloride solution. The solution was dried over sodium sulphate and evaporated. The pure ester was obtained by chromatography over bond-elute (eluents: CH_2Cl_2, 2 and 4% MeOH in CH_2Cl_2) (17 mg, 31% yield).

HNMR (δ, $CDCl_3$): 7.78 (1H, broad signal), 7.23-7.34 (5 H, m), 6.28-6.29 (2H, broad signal), 5.70-5.87 (1H, broad signal), 5.21 (1H, broad signal), 4.21-4.48 (6H,

two multiplets), 3.20 (2H, broad signal), 2.35 (2H, t, J = 7.7 Hz), 1.45-1.65 (13H, m), 1.26-1.38 (2H, m).

EXAMPLE 59

5-(Benzyl-*tert*-butoxycarbonyl-amino)-pentanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester



(111)

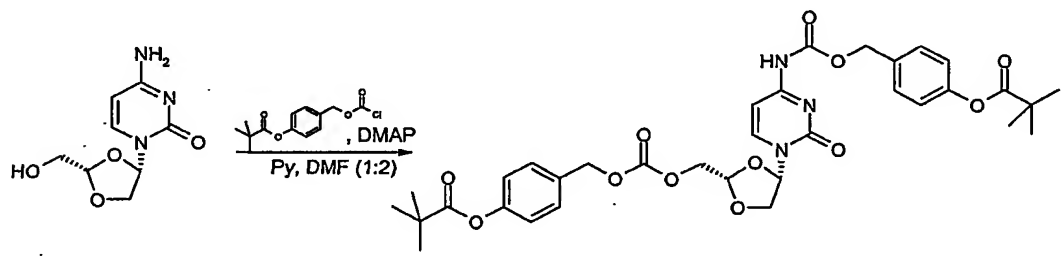
Procedure:

4-Amino-1-2-hydroxymethyl-[1,3]dioxolan-4-yl)-1*H*-pyrimidin-2-one (0.06 mmol) was treated 5-(Benzyl-tert-butoxycarbonyl-amino)-pentanoic acid (0.07 mmol) (Nucleosides, nucleotides & nucleic acids, 2000, 19 (7), 1057-1091), EDCI (0.09 mmol) and DMAP (catalytic amount) in DMF for 14 hours. The solution was neutralized with $NaHCO_3$ sat. and extracted with AcOEt. The combined organics layers was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by bond elute (2% $MeOH/CH_2Cl_2$ to 10% $MeOH/CH_2Cl_2$) to afford 36% of 5-(Benzyl-*tert*-butoxycarbonyl-amino)-pentanoic acid 4-(4-amino-2-oxo-2*H*-pyrimidin-1-yl)-[1,3]dioxolan-2-ylmethyl ester.

HNMR ($CDCl_3$) 7.86 (d, J= 6.4 Hz, 1H), 7.34-7.19 (m, 5H), 6.28 (broad s, 2H), 6.00 (d, J= 6.9 Hz, 1H), 5.07 (s, 2H), 4.50-4.31 (m, 3H), 4.28-4.15 (m, 3H), 3.18-3.08 (m, 2H), 2.17-2.16 (m, 2H), 1.60-1.40 (m, 13H).

EXAMPLE 60

2,2-Dimethylpropionic acid 4-(1-{2-[4-(2,2-dimethylpropionyl oxy)benzyloxy carbonyloxymethyl]-[1,3]dioxolan-4-yl}-2-oxo-1,2-dihydropyrimidin-4-ylcarbamoyloxymethyl)-phenyl ester (212)



Procedure:

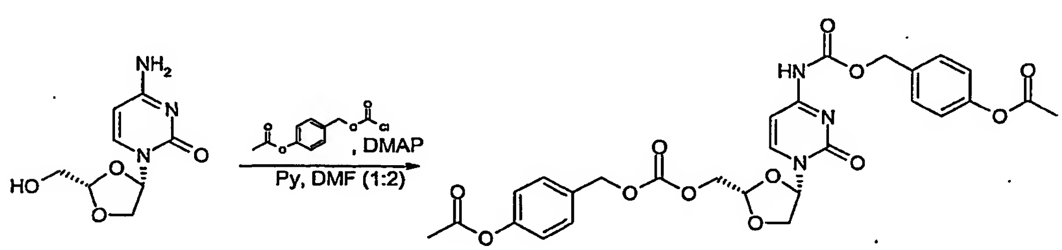
2,2-Dimethylproprionyloxybenzylchloroformate (1.56 mmol) was added dropwise to a 0°C solution of BCH-4556 (1.30 mmol) and DMAP (1.56 mmol) in dimethylformamide and pyridine and stirred at room temperature for 18h. The reaction mixture was concentrated in vacuo. The oil obtained was partitioned between NH_4Cl_{sat}/water and dichloromethane. Aqueous layer was extracted with DCM. Organic layers were combined, dried over $MgSO_4$, filtered and concentrated to a yellow gum. The crude residue was purified by silaca gel biotage (40S) (40 % EtOAc: 60% hexanes to 80 % EtOAc: 20 % hexanes) to give 1 % yield of 2,2-Dimethylpropionic acid 4(1-{2-[4-(2,2-

dimethylpropionyloxy) benzyloxycarbonyloxymethyl]-[1,3]dioxolan-4-yl}-2-oxo-1,2-dihydropyrimidin-4-ylcarbamoyloxymethyl)-phenyl ester (212) as a white powder.

^{1}H NMR (400 MHz, $CDCl_3$), δ ppm: 8.16 (d, 1H, J = 7.5Hz), 7.42-7.38 (m, 4H), 7.23 (d, 1H, J = 7.5Hz), 7.09-7.06 (m, 4H), 6.22-6.21 (m, 1H), 5.24-5.22 (m, 1H), 5.21 (s, 2H), 5.18 (s, 2H), 4.60 (dd, 1H, J = 2.6, 12.6Hz), 4.41 (dd, 1H, J = 2.4, 12.6Hz), 4.30-4.21 (m, 2H), 1.36 (s, 9H), 1.34 (s, 9H).

EXAMPLE 61

Acetic acid 4-(1-{2-[4-(Acetyloxy)benzyloxycarbonyl oxymethyl]-[1,3]dioxolan-4-yl} 2-oxo-1,2-dihydropyrimidin-4-ylcarbamoyloxymethyl)-phenyl ester (202)



Procedure:

Acetyloxybenzylchloroformate (1.14 mmole, 1,2 eq.) was added dropwise to a 0°C solution of BCH-4556 (0,952 mmole, 1 eq.) and DMAP (1,14 mmole, 1,2 eq.) in dimethylformamide and pyridine and stirred at room

temperature for 18h. The reaction mixture was concentrated in vacuo. The oil obtained was partitioned between saturated NH_4Cl and dichloromethane. Aqueous layer was extracted with dichloromethane. Organic layers were combined, dried over $MgSO_4$, filtered and concentrated to a yellow gum. The crude residue was purified by silica gel biotage (40S) (50% EtOAc: 50% hexanes to 100% EtOAc) to give 20,2 mg (4% yield) of the desired product.

^1H NMR (400 MHz, $CDCl_3$), δ ppm: 8,14 (dd 1H, J = 7,5 and 5,2 Hz), 7,64 (s 1H), 7,40 (m 4H), 7,24 (m 1H), 7,10 (m 4H), 6,20 (t 1H, J = 5,0 Hz), 5,19 (m 5H), 4,58 (m 2H), 2,30 (s 3H), 2,28 (s 3H).

Example 62

Cell Proliferation Assays/ NT Inhibitor Studies

The chemosensitivity of suspension cells lines (*e.g.*, CEM or CEM-derivatives) is assessed using the CellTiter 96□ proliferation assay. Cells are seeded in 96-well plates (8 replicates) in three separate experiments and exposed to graded concentrations (*e.g.*, 0.001-100 μM) of a nucleoside of interest (*e.g.*, cytarabine, gemcitabine or troxacitabine), for 48 h. Chemosensitivity is expressed as 50% (EC_{50}) of the dose response curve determined, *e.g.*, using GraphPad Prism 2.01 (GraphPad Software, San Diego, CA). Adherent cell lines (*e.g.*, DU145 or $DU145^R$) are seeded (~10^5 cells) in triplicate dishes, 24 h before drug exposure. Growth inhibition is determined by trypsinization and counting cells electronically.

In this example, troxacitabine is shown to enter cells by a mechanism other than via the NT, *es* (defective in CEM/ARA89C), or via the four other NTs which are not present in CEM cells, *ei*, *cit*, *cif*, and *cib* (See, *e.g.*, Ullman (1989). *Advances in Experimental Medicine & Biology* 253B: 415-20). This is consistent with entry into the cells by passive diffusion. The ability of troxacitabine to inhibit cell proliferation of CEM and CEM-derivative cell lines was directly compared to other cytosine-containing nucleoside analogs, gemcitabine and cytarabine, in a cell proliferation assay (See Table 1). The growth of CEM cells was inhibited by all three nucleoside analogs, and troxacitabine was 16 and 8-fold less toxic than cytarabine and gemcitabine, respectively. The presence of the *es* transport inhibitor, NBMPR, significantly increased resistance of CEM cells to gemcitabine and cytarabine but not to troxacitabine. CEM cells are reported to exhibit primarily *es*. Therefore, this example suggests that that the uptake of troxacitabine is less dependent on the presence of a functional hENT1 transporter (*es*) in CEM cells than cytarabine or gemcitabine. In addition, there was a much lower level of resistance observed for the nucleoside-transport deficient CEM/ARAC8C cells exposed to troxacitabine (8-fold) compared to cytarabine (1150-fold) or gemcitabine (431-fold), further implying lack of transport of troxacitabine (by es NT). Taken together, the data suggested that troxacitabine has a different uptake mechanism than cytarabine and gemcitabine. This again is consistent with entry into the cells by passive diffusion.

Table 1. Comparative chemosensitivities of CEM and CEM-derivative cell lines to troxacitabine, gemcitabine and cytarabine.

Cultures were exposed to graded concentrations (0.001-100 μM) of cytarabine, gemcitabine or troxacitabine for 48 h. Chemosensitivity was measured using the Promega CellTiter 96 cell proliferation assay and expressed as 50% of the dose response curve (EC_{50}). The effect of the es transport inhibitor, NBMPR (100 nM) on the EC_{50} values of CEM cells exposed to cytarabine, gemcitabine or troxacitabine was also determined. Each value represents the average ($\pm$ standard deviation) of three separate experiments (each experiment had 8 replicates).

Cell line	**Cytarabine**	**Gemcitabine**	**Troxacitabine**
CEM	0.01 $\pm$ 0.002	0.02 $\pm$ .0004	0.16 $\pm$ 0.012
CEM + NBMPR	0.05 $\pm$ 0.006	0.07 $\pm$ 0.018	0.21 $\pm$ 0.019
CEM/ARAC8C	11.50 $\pm$ 2.654	8.63 $\pm$ 0.881	1.18 $\pm$ 0.315
CEM/dCK$^-$	>50	>50	>100

EXAMPLE 63

Cellular Uptake Assays.

Measurements of nucleoside uptake are performed by conventional methods, as described, *e.g.*, in Rabbani *et al.* (1998) *Cancer Res.* 58: 3461; Weitman *et al.* (2000). *Clinical Cancer Res.*, 6:1574-1578; or Grove *et al.* (1996). *Cancer Res.*, 56: 4187-4191. Briefly, for adherent cells, uptake assays are conducted at room temperature under zero-trans conditions in either sodium-containing transport buffer (20 mM Tris/HCl, 3 mM K_2HPO_4, 1 mM $MgCl_2.6H_2O$, 2 mM $CaCl_2$, 5 mM glucose and 130 mM NaCl, pH 7.4, 300 $\pm$ 15 mOsm) or sodium-free transport buffer with NaCl replaced by N-methyl-D-glucamine. Cells are washed twice with the appropriate transport buffer and then either processed immediately, or in some experiments, incubated with transport inhibitors, NBMPR (100 mM), dipyridamole (20 μM) or dilazep (100 μM) during the second wash at room temperature for 15 min before the uptake assay. Precisely timed intervals are initiated by adding transport buffer containing [^{3}H]troxacitabine or [^{3}H]uridine and terminated by immersion in ice-cold transport buffer. After the plates are drained, the cells are lysed with 5% Triton X-100 and mixed with Ecolite scintillation fluid to measure the cell-associated radioactivity (Beckman LS 6500 scintillation counter; Beckman-Coulter Canada, Mississauga, ON). Uptake at the zero time-point is determined by treating cells for 10 min at 4°C with transport buffer containing 100 μM dilazep, then adding the radioactive nucleoside for 2 s before reaction termination as described above. Uptake assays for suspension cells

are conducted in microfuge tubes and permeant fluxes are terminated using the "inhibitor-oil" stop method; dilazep is used at a final concentration of 200 μM. Uptake at the zero time-point is determined by adding cells to cold transport buffer containing radiolabeled permeant and dilazep, and immediate centrifugation. Cell pellets are lysed and cell-associated radioactivity measured.

EXAMPLE 64

NT Inhibitor Studies/ Competition with an excess of the nucleoside of interest, itself, in non-radioactive form

CEM cells: CEM cells contain primarily one type of nucleoside transport activity (*es*), and the functionality of this transporter (hENT1) was first demonstrated by the uptake of the physiological substrate, uridine (Fig.1A), using methods as described in Example 29. The transport of [^{3}H]uridine was inhibited in the presence either of the hENT1 inhibitor, NBMPR, or excess non-radioactive uridine. [^{3}H]troxacitabine was taken up to a lesser degree over the 6-min time course in CEM and in CEM/ARAC8C cells (Fig. 1B). Lack of [^{3}H]uridine uptake in the latter cell line demonstrated the absence of functional hENT1 transporters. The data suggest that troxacitabine uptake in CEM cells is not mediated by *es* activity and is consistent with it being taken up by passive diffusion.

DU145 cells: The presence of functional *es*-mediated transport (hENT1) in DU145 cells was first demonstrated in a cellular uptake assay with 10 μM [^{3}H]uridine, as a control substrate in the presence and absence of the hENT1 inhibitor, NBMPR. In the presence of NBMPR, total [^{3}H]uridine uptake over a 6-min time course was inhibited by ~75% (Fig. 2A). In contrast, low levels of [^{3}H]troxacitabine were taken up and uptake was not affected by the presence of NBMPR (Fig. 2B). The results are consistent with the uptake of troxacitabine observed in CEM cells and provide further evidence that troxacitabine is a very poor substrate for hENT1, and probably enters the cell by passive diffusion.

HeLa cells: [^{3}H]Troxacitabine and [^{3}H]uridine cellular uptake by hENT2 (*ei* NT) in HeLa cells. In the presence of the hENT1 inhibitor, NBMPR, the functionality of hENT2 was first demonstrated in a cellular uptake assay with 10 μM [^{3}H]uridine (Fig.3A). A high total uptake of uridine was observed over a long time course of 240 min of about 1200 pmol/10^6 cells. In an expanded scale over the same time period, low levels of [^{3}H]troxacitabine were taken up with a total uptake of about 10 pmol/10^6 cells, 120-fold lower than uridine (Fig 3B). In the presence of nucleoside transport inhibitors, NBMPR, dilazep, and dipyridamole or excess non-radioactive troxacitabine, no substantial inhibition of troxacitabine uptake was observed. Taken together, the results demonstrate that compared to uridine, troxacitabine is a very poor substrate for hENT2. Furthermore, the fact that an excess of unlabeled troxacitabine failed to inhibit the uptake of the labeled troxacitabine indicates that troxacitabine is

not mediated by a nucleoside transporter, *i.e.*, that it enters the cells by passive diffusion.

DU145 cells: This experiment is designed to show whether $[^3H]$L-troxacitabine (10:M) is taken up by DU145 cells and if the rate of uptake is affected by the addition of high concentrations (1 mM) of non-radioactive troxacitabine. The results show that the uptake of $[^3H]$L-troxacitabine is very slow during both short (0-30s) and prolonged exposures (0-4 h). The addition of non-radioactive troxacitabine has no significant effect on the uptake of $[^3H]$L-troxacitabine, an indication that uptake in these cells is not mediated by a NT, but instead is taken up by passive diffusion.

EXAMPLE 65

Uptake by hCNT1, hCNT2 and hCNT3

[^{3}H]Troxacitabine and [^{3}H]uridine uptake by recombinant hCNT1 and hCNT2 in transient-transfection assays in HeLa cells:

Expression plasmids encoding recombinant hCNT1 and hCNT2 are prepared using conventional methods. Genes encoding the hCNT1 and hCNT2 transporter proteins are subcloned from the plasmids pMHK2 (Ritzel *et al.* (1997). *Am. J. Physiology* 272: C707-C714) and pMH15 (Ritzel *et al.* (1998). *Mol Membr Biol.* 15: 203-11) into the mammalian expression vector, pcDNA3, to produce pcDNA3-hCNT1 (Graham *et al.* (2000). *Nucleosides Nucleotides Nucleic Acids* 19: 415-434) and pcDNA3-hCNT2. The expression vectors are separately introduced into actively proliferating HeLa cells, following conventional methods. See, *e.g.*, Fang *et al* (1996). *Biochemical Journal* 317: 457-65.

Recombinant hCNT1 and hCNT2 were separately introduced into HeLa cells by transient transfection of pcDNA3 plasmids containing the coding sequences of the relevant nucleoside transporter protein. After transfection, functionality of each transporter was demonstrated by comparing the uptake of 10 μM [^{3}H]uridine in the presence of the equilibrative transporter (hENT1, hENT2) inhibitor, 100 μM dilazep, to cells transfected with the empty vector pcDNA3 control plasmid (Fig. 4). Uptake of

10 μM [^{3}H]troxacitabine was not mediated either by hCNT1 or by hCNT2.

Troxacitabine uptake by *cib*-activity (hCNT3) in differentiated HL-60 cells:

The ability of a high concentration (100-fold) of non-radioactive troxacitabine to inhibit the uptake of [^{3}H]uridine by hCNT3 was examined in a differentiated HL-60 model system [Ritzel *et al*. (2000), *supra*]. Under these conditions, troxacitabine had no effect on uridine uptake and suggested that troxacitabine was not substrate of hCNT3.

The examination of troxacitabine uptake in several cell lines has shown that uptake is not mediated by any of the characterized equilibrative (hENT1, hENT2) or sodium-dependent (hCNT1, hCNT2, hCNT3) nucleoside transporters. The low uptake observed for troxacitabine is consistent with a diffusion model.

Table of IC50 Values (μM) for Controls

Exposition of 24hr to drug, wash, incubated for another 48hr

(total of 72hr assay)

(3H-Thymidine Incorporation Assay)

IC50 in μM (3H-TdR incorporation at 72hr)

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
Gem citabine	0.0084	0.0090	0,0030	0.0035	51	14 571
	0.0140	0.0048	0,0110	0.0064	51	7 969
	0.0420	ND	0,0094	0.0034	30	8 824
	0.0083	0.0019	0,0077	0.0086	41	4 767
	0,0066	0.0083	0,0073	0.0092	30	3 260
	0.0100	0.0024	0,0110	0.0048	77	16 041
	0.0110	0.0049	0,0100	0.0094	85	9 043
	0,0160	0,0093	0,0130	0,0100	86	8 600
	0,0094	0,0100	0,0140	0,0086	80	9 302
	0,0097	0,0086	0,0100	0,0092	>100	10 870
	0,0110	0,0056	0,0091	0,0100	91	9 100
	0,0110	0,0060	0,0094	0,0092	93	10 109
	0,0110	0,0087	0,0090	0,0084	92	10 952
	0,0130	0,0120	0,0081	0,0120	>100	>8 333
	0,0041	0,0087	0,0045	0,0028	41	14 643
	0,0079	0,0059	0,0075	0,0079	87	11 013
	0,0055	0,0031	0,0045	0,0200	61	3 050
	0,0110	0,0100	0,0083	ND	88	ND
	0,0100	0,0094	0,0100	0,0061	66	10 820
	0,0091	0,0029	0,0037	0,0051	34	6 667
	0,0074	0,0051	0,0089	0,0090	40	4 444
	0,0091	0,0068	0,0078	0,0096	48	5 000
	0,0100	0,0089	0,0086	0,0100	72	7 200
	0,0110	0,0034	0,0100	0,0099	36	3 636
	0,0083	0,0041	0,0029	0,0073	>100	>13700
AVERAGE	0,011±0,007	0,0068±0,0028	0,0086±0,0027	0,0084±0,0035	66±24	8618±3614

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK- 24h	Factor*
Cytosine Arabinoside	0.0140	0.0088	0.140	0.0024	21	8 750
	0.0190	0.0220	0.450	0.0034	24	7 059
	0.0500	ND	0.470	0.0030	23	7 667
	0.0100	0.0098	0.077	0.0028	18	6 428
	0.0130	0.0100	0.320	0.0037	19	5 135
	0.0130	0.0140	0.033	0.0032	29	8 906
	0.0160	0.0160	0.300	0.0049	27	5 510
	0,0360	0,0170	0,300	0,0068	32	4 706
	0,0078	0,0200	ND	0,0280	>100	6 250
	0,0990	0,1000	2,100	0,0370	>100	2 700
	0,1500	0,1500	1,900	0,0350	>100	2 857
	0,1200	0,1700	0,890	0,0410	>100	2 439
	0,0990	0,1000	3,600	0,0250	>100	4 000
	0,1400	0,1500	1,200	0,0470	>100	>2 128
	0,0350	0,0960	0,120	0,0089	>100	>11 236
	0,0160	0,1100	1,600	0,0590	>100	1 695
	0,0540	0,0340	0,930	0,0084	>100	>11 905
	0,1100	0,1000	2,600	ND	>100	ND
	0,0750	0,0810	1,100	0,0100	41	4 100
	0,0160	0,0095	0,770	0,0056	41	7 321
	0,0200	0,0210	0,660	0,0094	40	4 255
	0,0160	0,0270	0,920	0,0092	78	8 478
	0,0780	0,0520	0,720	0,0100	59	5 900
	0,0370	0,0120	0,490	0,0071	40	5 634
	0,0250	0,0310	0,110	0,0053	75	14150
AVERAGE	0,052±0,045	0,061±0,052	0,94±0,89	0,016±0,017	62±35	5872±2783

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
BCH-4556	0,040 (72h)	0,066 (72h)	0,096 (72h)	0,076 (24h)	>100	>1315
	0.130	0.005	0.27	0.045	(24h)	1 244
	0.140	0.140	0.33	0.040	56	2 500
	0.049	ND	0.43	0.091	>100	1 099
	0.110	0.140	0.17	0.073	>100	1 370
	0.086	0.180	0.24	0.065	>100	1 538
	0.150	0.190	0.68	0.120	>100	833
	0.110	0.200	0.33	0.099	>100	1 010
	0,170	0,160	0,41	0,080	>100	1 250
	0,100	0,420	ND	0,028	>100	3 571
	0,140	0,160	0,40	0,100	>100	1 000
	0,180	0,340	0,74	0,096	>100	1 041
	0,140	0,015	0,15	0,100	>100	1 000
	0,110	0,310	0,71	0,083	>100	1 200
	0,160	0,280	0,49	0,130	>100	>769
	0,100	0,150	0,19	0,013	>100	>7 692
	0,140	0,210	0,63	0,063	>100	>1 587
	0,078	0,097	0,51	0,021	>100	>4 762
	0,150	0,220	0,66	ND	>100	ND
	0,160	0,140	0,59	0,072	>100	>1 389
	0,110	0,150	0,47	0,086	>100	>1 163
	0,130	0,220	0,66	0,059	>100	>1 695
	0,110	0,170	0,38	0,100	>100	>1 000
	0,130	0,220	0,53	0,074	>100	>1 351
	0,100	0,043	0,36	0,087	>100	>1 150
	0,180	0,031	0,11	0,0053	>100	>1 136
					>100	
	0,12±0,03	0,18±0,10	0,44±0,18	0,078±0,028	>100	1792±1584
27	0,0053 (72h)	0,0073 (72h)	0,023 (72h)	nd	nd	nd

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
275	0,0012 (72h)	0,0044 (72h)	0,013 (72h)	0.0056	51.6	9,214
276	0.025 (72h)	0.0017 (72h)	0,018 (72h)	0.028	26.8	957
277	0.20 0.29	0.013 0.016	0.21 0.19	0.049 0.100	>100 >100	2 040 >1 000
278	0.0024 (72h) 0,079	0.023 (72h) 0,038	0,013 (72h) 0,093	0,028 0,028	71,2 91	2543 3250
279	0,073 (72h) 0,58	0,021 (72h) 0,24	0,044 (72h) 0,39	0,026 0,083	48,2 >100	1854 >1205
280	1.9	3.1	18	1.9	>100	>53
38	0.34	1	0.90	0.11	>100	909

COM- POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/- dCK- 24h	Factor*
39	0.16 0.12	0.38 0.12	0.32 0.39	0.047 0.062	>100 >100	2 128 1 667
40	0.32	0.070	0.90	0.089	>100	1,123
41	40	91	>100	21	>100	5
42	0.010 0.007	0.014 0.005	0.022 0.026	0.0022 0.0023	82 >100	37 272 43 378
43	0.010	0.0041	0.029	<0,0001	>100	1,000,000
44	0.37	0.97	0.89	0.077	>100	1,300
45	3.2	2.7	9	1.6	>100	63

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
46	0.086	0.16	0.56	0.060	>100	1,667
47	1.8	2.4	38	2.9	>100	34
48	0,34 0,59	1,2 4,7	0,56 23	0,17 3,5	>100 >100	588 >29
49	4.5	8.8	7.1	0.57	>100	175
50	1.2	0.82	1.3	0.17	>100	588
51	0.83	0.57	0.86	0.024	47	1,958
52	0.0068	0.088	0.032	0.0012	0.48	400

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
53	8.9	10	10	2	37	19
54	0.17	0.50	0.70	0.12	65	542
55	0.029	0.0078	0.047	0.012	64	5,333
56	7	2	25	1.6	>100	63
57	0.0061	0.019	0.047	0.0048	32	6,667
58	0.012	0.016	0.13	0.014	38	2,714
59	1.4	0.19	0.69	0.54	>100	185

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
60	2,0 3,1	0,86 0,95	0,86 4,7	0,29 0,31	2,9 1,8	10 6
61	0.13 0.20 0.076	0.0770 0.0088 0.015	0.054 0.013 0.064	0.040 0.013 0.0074	>100 >100 >100	> 2 500 > 7 692 >13 513
62	0.89	1.7	4.3	0.35	>100	288
63	0.11	0.37	0.076	0.036	>100	2,778
64	0.0017	0.0044	0.0071	0.0018	3.6	2,000
65	0.011	0.012	0.033	0.0039	26	6,667
66	<0,00010 0.00025	<0,0001 0.000074	<0,0001 0.0011	<0,00010 0.000009	3 >0.1	>28 000 11 627

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
67	0.082	*ND*	0.40	0.18	>100	556
68	0.019	0.076	0.21	0.030	>100	3,333
69	0.045	0.028	0.050	0.0069	43	6,231
70	0.036	0.047	0.27	0.0088	30	3,409
71	0.31	0.13	0.81	0.18	>100	556
72	0.018 0.027	0.015 0.017	0.130 0.075	0.0160 0.0062	23 23	1 450 3 710
73	0.27	0.26	0.030	0.10	99	990

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
74	5.2	1.4	4.4	0.33	1.3	4
75	>100	64.00	>100	>100	>100	1
76	>100	>100	>100	>100	>100	1
77	0.059	0.030	0.38	0.054	74	1,370
78	0.042	0.045	0.095	0.037	13	351
79	0.12	0.17	0.16	0.014	63	4,500
80	1.8	0.67	3.5	0.46	>100	217

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
81	3.1	2.2	7.9	1.2	>100	83
82	0.17	0.12	0.30	0.053	>100	1,887
83	0.054	0.083	0.26	0.022	>100	4,545
84	0.014	0.0094	0.36	0.012	60	5,000
85	0.69	6.8	16	2.6	>100	38
86	0.0020	0.0019	0.013	0.0011	4	3,636
87	0,41 1,2 0,48	0,6 1,9 1,2	0,65 5,2 1,9	0,10 0,42 0,39	>100 >100 >100	>1 000 >238 >256

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
88	0.14	0.19	0.61	0.088	82	931
89	3.8	0.22	11	2.5	>100	40
90	95	61	>100	65	>100	1.5
91	0.63	1.8	5.5	2.8	>100	36
92	2.1	1.6	4.2	1.3	>100	77
93	0.04 74	>100 13.6	>100 >100	19 4.2	>100 >100	>5 >24
94	0.025 14	24 13	38 92	17 6	51 85	3 16

COM- POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/- dCK- 24h	Factor*
95	<0.0001 nd	0.15 0.10	0.61 0.25	0.240 0.057	30 86	123 1 503
96	0.0061 1.5	0.19 0.21	1.4 9.6	1.8 1.9	>100 >100	>56 >52
97	N.D 22	5,0 4,0	56 25	9.2 5.9	>100 >100	>11 >19
98	nd 36 11	0.13 0.15 0.22	>100 2.2 2.3	35 22 61	>100 >100 >100	>3 >4 >3
99	N.D.	6.3	33.0	5	>100	>20
100	nd 0.030 0,044 nd	2.70 1.40 0,96 0,25	4.80 0.09 5,80 1,00	2.70 0.52 2,50 0,64	19 55 45 15	7 105 18 23
101	0.33	0.41	2.1	0.36	16	44

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
102	0.19	1.7	1.0	0.41	11	27
103	0.052	0.018	0.063	0.011	50	4,545
104	0.27	0.47	0.47	0.21	>100	>476
105	0.080	0.068	0.071	0.033	79	2 393
106	0.014	0.037	0.095	0.010	46	4,600
107	0.0280 0.0094 0.0340 0,0200 0,0037 0,0084	0.012 0.019 0.030 0,013 0,023 0,035	0.220 0.078 0.034 0,068 0,071 0,260	0.0120 0.0056 0.0088 0,0200 0,0140 0,0210	37 30 83 82 59 20	3 100 5 428 9 432 4 100 4 214 952
108	1.8	27	3.8	3.4	>100	>29

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
109	2.6	31	4.8	1.0	>100	>100
110	0.0010	0.010	0.0049	0.0013	4.3	3 307
111	0.00013	0.00026	0.0021	0.00020	2.6	13000
112	0.011	0.016	0.0067	0.0058	0.057	10
113	0.24	0.48	1.1	0.060	>100	>1 667
114	0.066	0.017	0.041	0.016	8	500
115	0.38	0.15	0.62	0.20	>100	>500

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
116	1.4	0.11	2.5	0.38	>100	>263
117	0.46	0.46	0.68	0.18	89	494
118	0.022	0.077	0.16	0.028	>100	>3 571
119	17	27	94	56	96	~2
120	>100	64	>100	>100	>100	1
121	28	37	>100	17	>100	>6
122	1.9	0.21	0.57	0.71	61	86

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
123	1.0	1.4	2.0	0.87	15	17
124	13	14	49	14	27	~2
125	0.24	0.016	0.60	0.072	7	97
126	0.0041	0.0020	0.0085	0.0016	13	8,125
127	35.0 4,9	16 15	23 >100	15 22	>100 >100	>7 >4,5
128	0.14	0.090,	0.17	0.22	>100	>454
129	0.15	0.020	0.20	0.072	15	208

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
130	0.058	0.050	0.11	0.057	75	1,316
131	0.11	0.10	0.012	0.021	83	3,952
132	0.0021 0.0190 0,0130 0,0016	0.0011 0.0200 0,0130 0,0010	<0.0001 0.0180 0,0130 0,0045	<0.00010 0.00091 0,00370 <0.00010	8 >1 11 10	>80 000 >1 100 2 973 >100 000
133	0.021	0.10	0.016	0.027	31	1,148
134	12	11	3	7	20	3
135	0,15 9,00	0,23 11,0	0,25 ND	0,097 4,1	59 19	608 5
136	9	12	3	4	>100	>25

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
137	6.00 0,35	17.0 5,1	18,4 16.0	5.0 6,5	84 53	17 8
138	0.92	1.5	2.1	0.53	58	109
139	0.81 0.51	1.4 1.7	1.3 1.7	0.40 0.42	>100 >100	>250 >250
140	10	20	3	11	>100	>9
141	0.034	0.066	0.040	0.019	69	3,632
142	0.038	0.029	0.13	0.0072	46	6,389
143	0.012	0.0037	0.14	0.0039	32.0	8,205

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
144	3	5.2	1.9	0.71	78	110
145	0.24	0.77	0.12	0.084	69	821
146	0.78	1.2	0.028	0.13	50	385
147	0.060	0.11	0.017	0.025	>100	>4 000
148	36	6.30	9.90	6.3	24	4
149	<0.0001 0.0028	0.00150 0.00039	<0.0001 0.0070	<0.00010 0.00012	2 >1,8	>19 000 >15 000
150	0.96	1.6	1.3	0.13	90	692

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
151	9.7	8.3	4.4	0.59	>100	>169
152	3.5	3.0	31.00	0.79	>100	>127
153	46	39	59	0.21	>100	>476
154	0.76	1.6	4.4	0.14	>100	>714
155	1,6 0,093 0,43	3,7 0,060 0,76	5,9 0,97 1,7	0,10 0,15 0,54	>100 >100 >100	>1 000 > 667 > 185
156	0.12	0.068	0.93	0.0070	81	11,571
157	0.024	0.55	2.2	0.012	>100	>8 333

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
158	0.63	0.040	3.7	0.094	58	617
159	0.87	0.72	1.6	0.38	>100	>263
160	0.92	0.36	1.2	0.36	>100	>278
162	8.4 6.4 9,2 2,9	9.4 3.9 5,7 3,6	1.1 7.0 12 17	2.2 2.8 3,3 4,1	>100 >100 >100 >100	>44 >36 >30 >24
163	0.0092	0.033	0.025	0.0033	27	8,182
164	0.13	0.14	0.28	0.060	>100	1 667
165	3.4	10	16	1.8	>100	>56

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK- 24h	Factor*
166	0.0073 0.0044 0,0180 0,0170	0.0012 0.0014 0,0090 0,0110	0.0046 0.0092 0,0580 0,0640	0.0001 0.0077 0,0047 0,0024	10 >1 10 >100	>90 000 >130 2 128 >41 667
167	0,160 0,062 0,230	0,20 0,12 0,30	0,64 0,12 0,54	0,073 0,031 0,110	10 >100 12	137 3 225 109
168	96 25 45	16 2,4 44	98 31 59	31 22 20	>100 >100 >100	>3 >4 >5
169	8.2	5.1	7.1	2.0	>100	>50
170	0.63	0.49	1.0	0.21	>100	>476
171	45	41	82	38	>100	>2.6
172	0,014 0,015	0,019 0,036	0,0037 0,0210	0,0074 0,0085	2 5	270 588

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
173	6.1	17	2.0	2.6	>100	>38
174	11	21	38	9.0	>100	>11
175	6.3	3.1	32	3.5	>100	>29
176	0,040 0,043	0,094 0,032	0,057 0,032	0,014 0,011	38 68	2 714 6 182
177	0.19	0.22	0.92	0.095	>100	>1 052
178	88	5.8	41	25	>100	>4
179	1.7	2.8	0.56	2.4	>100	>42

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
180	>100	65	49	>100	>100	>1
181	0.14	0.49	0.17	0.037	>100	>2700
182	0.13	0.22	0.21	0.047	>100	>2100
183	0.037	0.038	0.12	0.018	45	2,500
184	0.94	0.92	1.1	0.81	40	49
185	0.059	0.064	0.054	0.066	17	258
186	<0.0001 <0.0001 0,0039	0,0300 0,0210 0,0062	0,0270 0,0017 0,0770	0,0087 0,0220 0,0049	>100 >100 >100	>11 494 > 4 545 >20 408

COM- POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/- dCK- 24h	Factor*
187	0,0014 0,0011	0,0042 0,0051	0,0200 0,0080	0,0017 0,0016	4,1 0,66	2 412 413
188	0,097 0,068 0,120	3,0 3,8 4,9	0,46 2,40 2,40	0,79 1,50 1,10	>100 >100 >100	>127 > 67 > 91
189	0,00120 0,00068	0,0033 0,0037	0,0092 0,0016	0,0021 0,0010	2,8 1,3	1333 1 300
190	0,0061 0,0039	0,027 0,016	0,0400 0,0056	0,0084 0,0036	22 9,8	2 619 2 722
191	<1E-04 <1E-11 ND	<1E-04 <1E-11 ND	<1E-04 <1E-11 ND	<1E-04 <1E-11 1,6E-11	0,54 >1E- 04 11	>5 400 >1E07 7,0E11
192	0.29	0.0016	0.40	0.0084	48	5,714
193	0.64	0.16	2.0	0.059	>100	>1 695

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
194	0.011	0.0040	0.041	0.0024	10	4 167
195	1.1	1.9	1.5	0.064	>100	>1 563
196	<1E-04 1.1E-08 ND	<1E-04 <1E-11 ND	<1E-04 2.5E-07 ND	<1E-04 <1E-11 1,2E-06	2,5 >1E-04 26	>25 000 >1E07 2,2E07
197	<1E-04 <1E-11 ND	<1E-04 <1E-11 ND	<1E-04 <1E-11 ND	<1E-04 <1E-11 ND	0,94 >1E-04 11	>9 400 >1E07 ND
198	<1E-04 1.4E-08 ND	<1E-04 1.2E-05 ND	<1E-04 1.0E-07 ND	<1E-04 1.1E-08 ND	2,1 >1E-04 17	>21 000 >10 000 ND
199	0.033	0.21	0.0078	0.0094	>100	>10 638
200	0.30	1.1	0.12	0.31	72	232

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
201	17	18	7.3	14	>100	>7
202	<1E-04 2,1E-05	<1E-04 ND	<1E-04 1,2E-05	<1E-04 ND	0,1 1,1	>1 000 ND
203	<1E-04 ND	<1E-04 ND	<1E-04 ND	<1E-04 3,3E-04	1,3 8,6	>13 000 26 060
204	0.015	0.0086	0.025	0.012	19	1 600
205	0.28	0.90	0.10	0.26	>100	>385
206	0.012	0.056	0.043	0.0090	80	8,889
207	0.0061	0.0044	0.0023	0.0027	15	5,556

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
208	<1E-04 0,0027	<1E-04 0,00063	<1E-04 0,0062	<1E-04 0,000052	1,42 11	>14 000 211 538
209	0.31	1.3	0.59	*ND*	>100	*ND*
210	0.0026	0.0050	0.26	*ND*	>100	*ND*
211	≤0,0001 0,0000086 0,0000400	≤0,0001 0,000015 0,000030	≤0,0001 0,00016 0,00087	*ND* 0,000027 0,000053	0,71 >1 >0,1	*ND* >3 704 >1 887
212	0.00011	0.00059	0.018	*ND*	3.5	*ND*
213	≤0,0001	0.00027	0.012	*ND*	1.1	*ND*
214	9.4	9.4	89	*ND*	>100	*ND*

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK- 24h	Factor*
215	3.9	33	96	*ND*	>100	*ND*
216	0.00088	≤0,0001	0.018	*ND*	14	*ND*
217	≤0,0001	≤0,0001	0.00013	*ND*	1.2	*ND*
218	0.0091	0.052	0.081	*ND*	60	*ND*
219	≤0,0001	≤0,0001	0.00012	*ND*	2.1	*ND*
220	0.0034	0.029	0.042	0.0035	>100	>28 571
221	0.43	0.39	1.6	0.13	>100	>769

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
222	0.21	0.19	0.85	0.11	>100	>909
223	0.035	0.15	0.25	0.062	>100	>1 613
224	5.3	6.9	21	0.10	>100	>1 000
225	11	11	43	0.88	>100	>113
226	0,00063 0,02600	0,0017 0,0330	0,035 0,016	0,00076 0,02100	28 >0,1	36 842 > 5
227	0.84	0.012	3.0	0.043	22	512
228	0.68	1.5	5.3	0.44	>100	>227

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
229	13 14	15 18	11 57	11 ND	>100 >100	> 9 ND
230	1.5	3.8	9.5	1.0	>100	>100
231	0.015	0.15	1.1	0.076	>100	>1 315
232	0,00053 0,00038	0,0096 0,0017	0,0190 0,0041	0,0037 0,0019	5,8 4,5	1 568 2 368
233	1,5 5,4 4,4	13 9,6 11	12 17 15	11 ND 9,7	18 18 22	1,7 ND 2
234	1.5	0.10	0.10	0.95	>100	>105
235	1.6	1.1	0.38	1.2	61	51

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
236	3.7	8.6	0.12	5.1	>100	>20
237	0.0026	≤0.0001	0.088	0.0016	18	11,250
238	0.00045	≤0.0001	0.025	0.0025	59	23,600
239	0.0065	0.00033	0.19	0.0030	20	6667
240	≤0.0001	≤0.0001	≤0.0001	≤0.0001	2.5	≥25 000
241	0.047	0.17	14	1.4	≥100	≥74
242	0.25	0.0010	1.1	0.23	93	404

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
243	0.0011	0.00050	0.32	0.027	72	2,667
244	1.9	0.019	26	11	≥100	≥9
245	<1E-4	<1E-4	<1E-4	<1E-4	0.68	>6 800
246	47	1.4	28	25	>100	>4
247	0.13	0.00078	0.13	0.10	15	150
249	8.6	0.78	8.4	3.9	>100	>25
250	0.17	0.16	0.17	0.063	31	492

COM-POUND	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/-dCK-24h	Factor*
254	0.17	0.18	0.29	0.098	31	316
256	4.6	5.1	14	5.3	20	4
257	9.7	5	1.6	4.2	>100	>24

*Resistance Factor = Ratio of dCK- on Wild-type CCRF-CEM

ND: Not Determined

NIH lines:

MCF-7: Human Breast Carcinoma

H-460: Human Lung Carcinoma

SF-268: Human Central Nervous System Tumor

CCRF-CEM: T-cell Leukemia

Dck-: CCRF-CEM deoxycytidine kinase-deficient

Table 2 of IC50 Values (μM) for Pro-drugs of BCH-4556 Exposition of 24hr to drug, washed, and incubated for another 48hr (total of 72hr assay)

IC_{50} μM (MTT at 72hr) IC_{50} μM (MMT or WST-1 at 72hr)

BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/dCK- 24h	RESISTANCE FACTOR*
Gemcitabine	0,012	0,0060	0,015	*ND*	>100	*ND*
	0,017	0,0092	0,064	0,0740	>100	>1 351
	0,086	0,2800	0,180	*ND*	>100	ND
	0,420	0,2600	0,220	0,0240	6,7	279
	0,046	0,0770	0,056	0,0250	19	760
	0,012	0,1100	0,048	0,0100	49	4 900
	0,086	0,0070	0,270	0,0071	34	4 789
	0,013	0,0150	0,082	0,0067	11	1 642
	0,014	0,0078	0,017	0,0088	56	6 364
	0,012	0,0120	0,840	0,0083	98	11 807
	0,070	0,1200	0,130	0,0051	65	12 745
	0,055	0,0270	0,023	0,0038	>10	>2 631
AVERAGE	0,072±0,126	0,078±0,107	0,18±0,25	0,020±0,023	57±39	3987±3871
Cytosine Arabinoside	0,150	0,110	4,1	*ND*	>100	*ND*
	0,088	0,058	26	0,0820	>100	>1 220
	0,250	0,510	7,2	*ND*	>100	ND
	0,780	0,920	73	0,0370	>100	>2 700
	0,130	0,210	39	0,0380	69	1 816
	0,063	0,830	16	0,0130	83	6 385
	0,180	0,054	42	0,0085	15	1 765
	0,081	0,056	15	0,0079	11	1 392
	0,066	0,050	1,9	0,0100	29	2 900

BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/dCK- 24h	RESISTANCE FACTOR*
	0,073	0,061	ND	0,0100	69	6 900
	0,350	0,860	7,8	0,0094	91	9 680
	0,095	0,160	5,9	0,0078	>10	>1 282
AVERAGE	0,19±0,22	0,29±0,34	25±23	0,026±0,026	68±36	3135±2246
BCH-4556	0,35	0,12	16	*ND*	>100	*ND*
	0,78	0,63	17	0,44	>100	>227
	3,50	3,20	9,8	*ND*	>100	ND
	5,10	7,70	45	0,72	>100	>139
	1,70	1,30	15	0,79	>100	>126
	0,51	3,30	32	0,14	>100	>714
	1,30	0,53	28	0,21	>100	>476
	0,76	0,51	19	0,21	10	48
	ND	ND	ND	ND	ND	ND
	0,54	0,72	83	0,14	>100	>714
	2,30	1,60	16	0,16	>100	>625
	0,78	1,50	7,1	0,14	>10	>71
AVERAGE	1,6±1,6	2,0±2,4	29±23	0,38±0,28	>100	349±283
277	2.0	0.32	7.3	0.48	>100	>208
107	0.27	0.25	3.4	0.024	49	2,042

BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/d CK- 24h	RESISTANCE FACTOR*
110 (HCl salt: 251)	0,01300 0,00049 0,00060	0,018 0,120 0,240	1,10 0,14 7,50	0,0034 0,0025 0,0040	1,3 7,1 9,4	382 2 840 2 350
172	0,21 2,70 3,30	0,17 1,30 0,97	0,76 9,70 54	0,09 0,28 0,20	1,3 32 80	14 114 400
185	0,86 1,70 1,80	1,4 1,4 2,3	4,9 5,9 17	0,18 0,18 0,45	12 12 30	67 67 67
186	0,0057 0,0270	0,047 3,4	1,7 >10	0,0086 0,0790	26 14	3 023 177
191	≤0,0001 0,0078 0,0017	≤0,0001 0,0041 0,0054	0,010 >0,1 0,065	*ND* 0,0029 0,0710	1,1 >0,1 12	*ND* >34 169
196	0,010 0,098	0,0010 0,0064	0,045 0,650	*ND* *0,010*	7,7 >1	*ND* *>100* *43*
197	≤0,0001 0,0097 0,0038	≤0,0001 0,00250 0,00014	0,01 >0,1 0,22	*ND* 0,0018 0,0530	7,4 >0,1 >100	*ND* >56 >1 886
198 (HCl salt: 261)	≤0,0001 0,0062 0,0068	0,0001 0,0028 0,0046	0,0054 >0,1 0,73	*ND* 0,0083 0,1400	10 >0,1 23	*ND* >12 164

BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/d CK- 24h	RESISTANCE FACTOR*
202	≤0,0001 0,021	0,0001 0,0850	0,043 >0,1	*ND* *0,014*	0,05 >0,1	*ND* >7
203	0,120 0,250 0,050	0,010 0,089 0,120	0,72 >1 7,4	*ND* 0,010 0,460	1,2 >1 20	*ND* >100 43
207	0,53 0,65	0,13 0,49	>1 >1	0,074 0,190	>1 >1	>14 >5
208	0,11 0,20	0,031 0,066	0,47 2,20	0,0590 0,0093	25 >1	424 >108
210	0,37 1,70 0,11 0,22	0,130 0,065 0,270 0,110	≥100 >100 51 >100	0,24 0,46 0,13 0,50	51 >100 >100 47	204 >217 >770 94
211 (HCl salt: 248)	0,0053 0,0030 0,0140 ND <1e-6 0,0087	0,00100 0,00015 0,00770 0,00013 <1e-6 0,00130	0,038 0,050 0,034 0,012 0,029 0,034	0,0028000 0,0350000 0,0003300 ND <1e-6 0,0000023	>1 13 >0,1 8,70 1,50 0,44	>357 371 >303 ND >1500000 >191 300
216	0.064	0.0094	0.40	0.34	31	91

BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/dCK- 24h	RESISTANCE FACTOR*
217	0.011	0.0039	0.12	0.36	27	75
219	0,014 0,058	0,0037 0,0220	0,18 1,60	0,018 0,010	51 >1	2833 > 100
223	1,70 0,78 4,00	1,7 2,1 1,4	15 47 45	0,12 0,13 0,45	>100 >100 >100	>833 >769 >222
226	0,850 0,250 0,065 0,420	0,40 0,26 0,22 0,14	>1 1,8 3,9 17	0,0600 0,0410 0,0011 0,0260	>1 >10 15 35	> 17 >244 13 636 1 346
232	0.0069	0.020	0.16	0.010	2.1	210
237	0,042 5,200 0,170	0,0011 0,0220 0,1700	3,3 1,8 2,7	0,0014 0,0100 0,0040	2,7 22 15	1 928 2 200 3 750
238 (HCl salt: 269)	0,064 0,046 0,017 0,062	0,00460 0,00130 0,00020 0,01000	5,7 1,9 5,6 2,7	0,0170 0,0050 0,0048 0,0014	23 10 5,2 28	1 353 2 000 1 080 20 000
239	0,49 0,20 0,20	0,0021 0,0031 0,6400	9,0 4,9 25	0,0045 0,0022 0,0110	20 28 17	4 444 12 727 1 545

BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/dCK- 24h	RESISTANCE FACTOR*
240	<1e-6	<1e-6	0,053	<1e-6	1,70	>1 700 000
(HCl salt: 264)	0,0091	0,00045	0,016	0,000011	0,11	10 000
	0,0014	0,00068	0,031	0,000029	0,84	28 965
	0,0069	0,00190	0,028	0,000002	1,40	700 000
243	0,140	0,00640	14	0,0480	30	625
(HCl salt: 260)	0,038	0,00079	7,7	0,0081	21	2 593
	0,024	0,12000	68	0,0400	51	1 275
245	0,00021	<1E-5	0,0440	<1E-5	2,2	>220 000
(HCl salt: 268)	0,00290	0,00300	0,0950	0,000021	3,4	161 904
	0,00110	0,00013	0,0047	>1E-6	6,0	>6E6
247	0,39	0,00089	6,1	0,024	61	2 542
	0,54	0,30000	>10	0,140	49	350
	0,46	0,01600	14	0,170	61	359
257	89	36	>100	4,1	>100	>24
	42	21	>100	5,4	>100	>19
262	0.90	16	>100	0.88	>100	>114
263	66	73	>100	19	>100	>5
	>100	12	>100	14	>100	>7
265	>100	77	>100	30	>100	>3

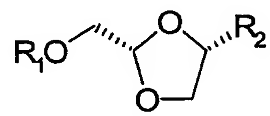
BCH	H-460 24h	MCF-7 24h	SF-268 24h	CCRF-CEM 24h	CEM/d CK- 24h	RESISTANCE FACTOR*
266	0,00690 0,00053	0,0120 0,0013	1,00 0,42	0,00190 0,00067	21 26	11 050 37 143
267	93	34	>10	2.9	>10	>3

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS:

1. A method of treating a patient having a cancer comprising administering to said patient a compound having the following formula:



(I)

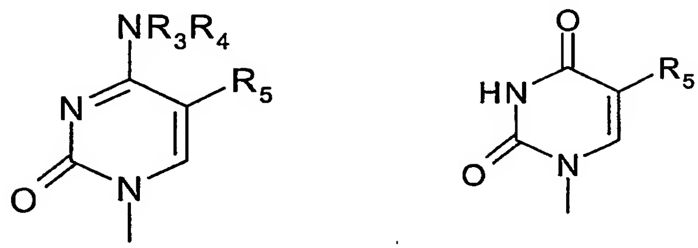
wherein:

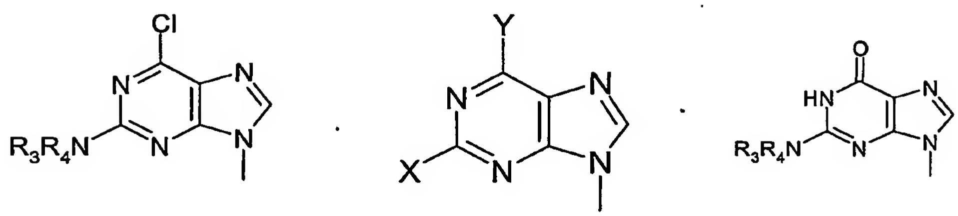
R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof, wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl; saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is





R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr,

Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; and

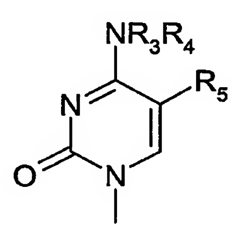
R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

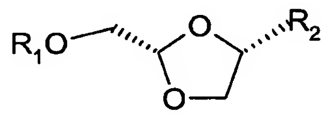
a pharmaceutically acceptable salt thereof.

2. A method according to claim 1, wherein at that least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$ or $-C(O)NHR_6$, then R_6 is other than H.

3. A method according to claim 1, wherein R_2 is of the formula:



4. A method of treating a patient with cancer, wherein the cancer cells are deficient in nucleoside or nucleobase transporter proteins, comprising administering to said patient a compound according to the following formula:



(I)

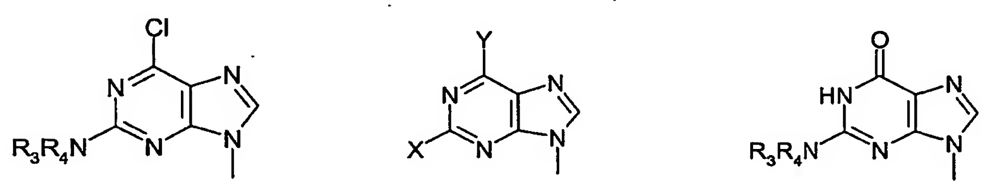
wherein:

R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_{6'}$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, or C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate or triphosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-18} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

a pharmaceutically acceptable salt thereof.

5. A method according to claim 4, wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$, or $-C(O)NHR_6$ then R_6 is other than H.

6. A method according to claim 4, wherein said cancer cells are deficient in one or more nucleoside or nucleobase transporter proteins that provide sodium-independent, bidirectional equilibrative transport.

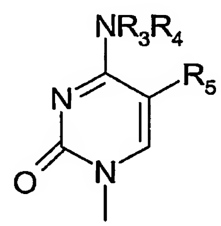
7. A method according to claim 4, wherein said cancer cells are deficient in nucleoside or nucleobase transporter proteins that provide sodium-dependent, inwardly directed concentrative processes.

8. A method according to claim 7, wherein said cancer cells are deficient in nucleoside or nucleobase transporter proteins that provide sodium-dependent, inwardly directed concentrative processes.

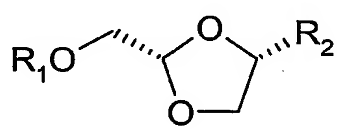
9. A method according to claim 4, wherein said cancer cells are deficient in es transporter proteins, ei transporter proteins or both.

10. A method according to claim 4, wherein said cancer cells are deficient in cit transporter proteins, cib transporter proteins, cif transporter proteins, csg transporter proteins, cs transporter proteins, or combinations thereof.

11. A method according to claim 4, wherein R_2 is of the formula:



12. A method of treating patients with cancer comprising administering to said patient a compound of the following formula:



(I)

wherein:

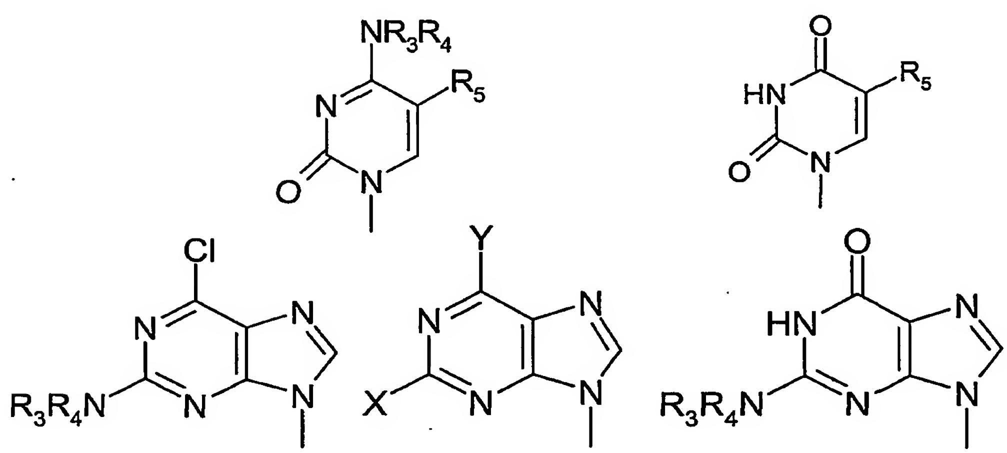
R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or a dipeptide or tripeptide

chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gly, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triophosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and at least one amino acid is not Gly, and which in each case is optionally terminated by -R_7;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, -C(O)R_6, -C(O)OR_6; and

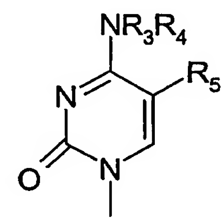
X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4;

with the proviso that least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$, or $-C(O)NHR_6$ then R_6 is other than H; or

a pharmaceutically acceptable salt thereof;

wherein said compound is administered at least daily for a period of 2 to 10 days.

13. A method according to claim 12, wherein R_2 is of the formula:



14. A method of treating a patient with cancer wherein the cancer is resistant to cytarabine, said method comprising administering to said patient a compound according to the following formula:

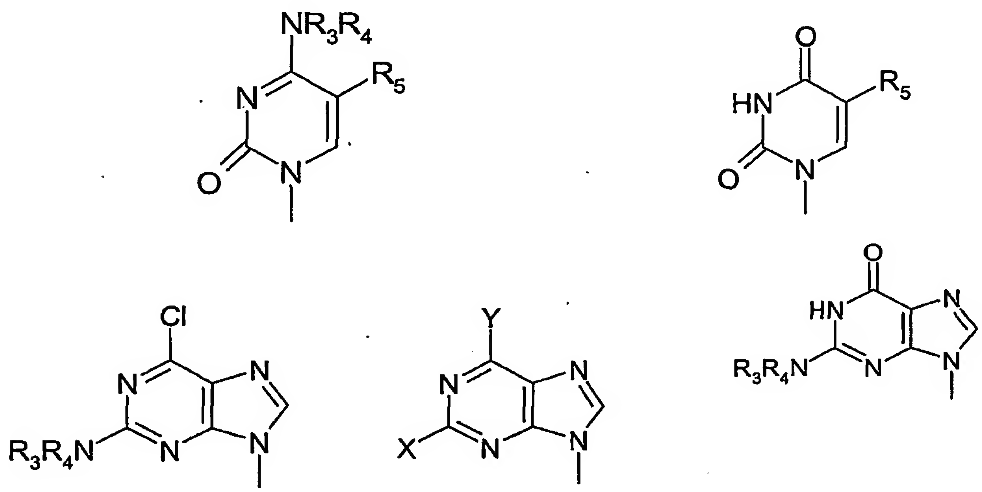
R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NRH_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and

Gln, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or a dipeptide or a tripeptide

chain or mimetic thereof wherein the amino acids are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-24} heteroaromatic ring, C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

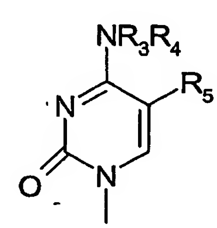
R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{5-24} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

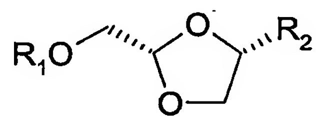
a pharmaceutically acceptable salt thereof.

15. A method according to claim 14, wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$; $-C(O)OR_6$, or $-C(O)NHR_6$ then R_6 is other than H.

16. A method according to claim 14, wherein R_2 is of the formula:



17. A method of treating a patient with cancer comprising:
determining that a compound enters cancer cells predominately by passive diffusion; and administering said compound to said patient; wherein said compound is a compound according to the formula:



(I)

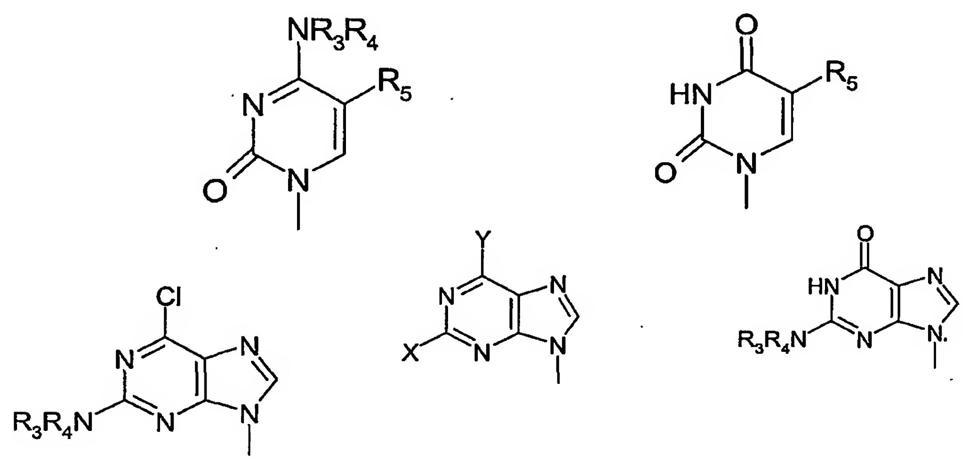
wherein:

R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R_7;

R_1 can also be a P(O)(OR')$_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-24} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{2-24} alkyl; C_{1-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-24} heteroaromatic ring, C_{3-20} non-aromatic ring

optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

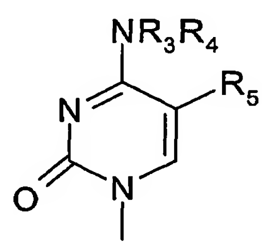
R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{5-24} heteroaromatic ring, C_{3-20} nonaromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

a pharmaceutically acceptable salt thereof.

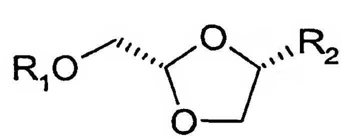
18. A method according to claim 17, wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$ or $-C(O)OR_6$, then R_6 is other than H.

19. A method according to claim 17, wherein R_2 is of the formula:



20. A method of treating a patient with cancer comprising:

administering to said patient a compound which has been determined to enter the cancer cells predominately by passive diffusion, wherein said compound is a compound according to the formula:



(I)

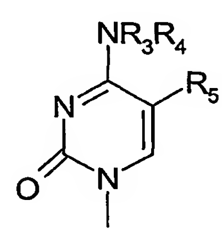
wherein:

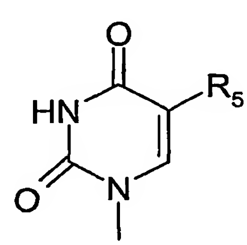
R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

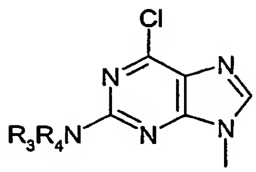
R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

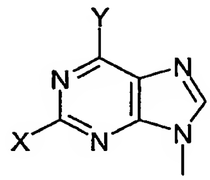
R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

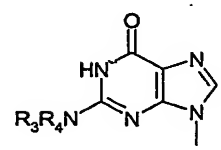
R_2 is











R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R_7;

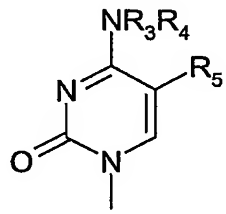
R_6 is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, -C(O)R_6, -C(O)OR_6; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or a pharmaceutically acceptable salt thereof.

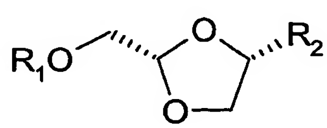
21. A method according to claim 20, wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$; $-C(O)OR_6$ or $-C(O)NHR_6$ then R_6 is other than H.

22. A method according to claim 20, wherein R_2 is of the formula:



23. A method of treating a patient with cancer resistant to troxacitabine, comprising administering to said patient a troxacitabine derivative having a greater lipophilicity than troxacitabine.

24. A method according to claim 23, wherein said derivative is a compound of the following formula:



(I)

wherein:

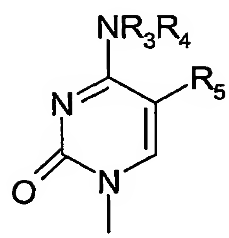
R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino

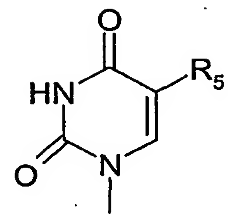
acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln and the amino acid chain contains at least one amino acid other than Gly, and which in each case is optionally terminated by $-R_7$;

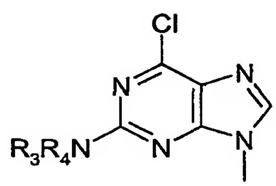
R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-24} arylmethyl, C_{2-17} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

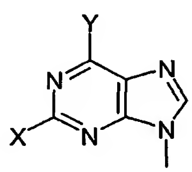
R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

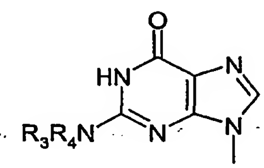
R_2 is











R_3 and R_4 are in each case independently H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R_6; -C(O)OR_6; -C(O)NHR_6; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln and the amino acid chain contains at least one amino acid other than Gly, and which in each case is optionally terminated by -R_7;

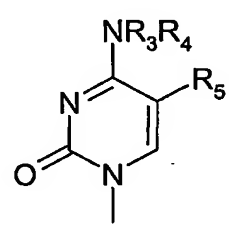
R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; with the proviso that least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$ or $-C(O)NHR_6$, then R_6 is other than H; or

a pharmaceutically acceptable salt thereof.

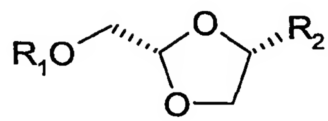
25. A method according to claim 24, wherein R_2 is of the formula:



26. A method of treating a patient with cancer comprising:

determining that a compound does not enter cancer cells predominately by nucleoside or nucleobase transporter proteins; and administering said compound to said patient;

wherein said compound is a compound according to the formula:



(I)

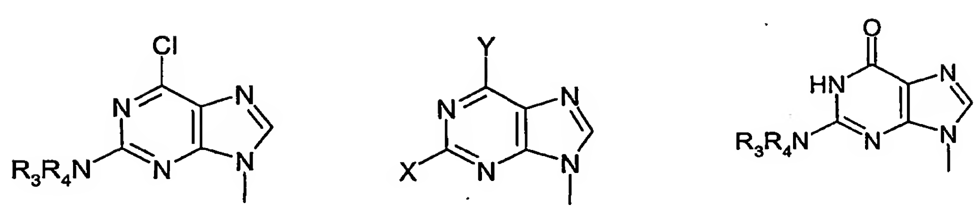
wherein:

R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-24} arylmethyl, C_{2-17} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl-C_{6-24} aryl, C_{0-20} alkyl-C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

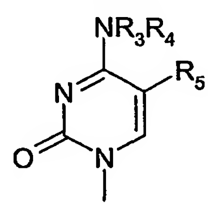
R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4;

or a pharmaceutically acceptable salt thereof.

27. A method according to claim 26, wherein at least one of R_1, R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$ or $-C(O)NHR_6$ then R_6 is other than H.

28. A method according to claim 27, wherein R_2 is of the formula:



29. A method according to any one of claims 1-28, wherein said cancer is prostate cancer, colon cancer, lung cancer, melanoma, ovarian cancer, renal cancer, breast cancer, lymphoma, pancreatic cancer or bladder cancer.

30. A method according to any one of claims 3-28, wherein said cancer is leukemia.

31. A method according to any one of claims 1-28, wherein at least one of R_1, R_3, or R_4 is piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, adamantyl or quinuclidinyl.

32. A method according to any one of claims 1-28, wherein at least one of R_1, R_3 or R_4 is acetyl, propionyl, butyryl, valeryl, caprioic, caprylic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, or linolenic.

33. A method according to any one of claims 1-28, wherein at least one of R_1, R_3 or R_4 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, napthyl or biphenyl.

34. A method according to any one of claims 1-28, wherein at least one of R_1, R_3 or R_4 contains a heterocyclic group selected from the following group: furyl, thiophenyl, pyrrolyl, imidazolyl, pyrazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, triazolyl, tetrazolyl, oxadrazolyl, thiadiazolyl, thiopyranyl, pyrazinyl, benzofuryl, benzothiophenyl, indolyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiozolyl, benzisothiazolyl, benzoxadiazolyl, quinolinyl, isoquinolinyl, carbazolyl, acridinyl, cinnolinyl and quinazolinyl.

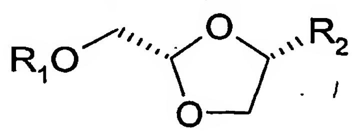
35. A method according to any one of claims 1-28, wherein said compound is administered at least daily for a period of 2 to 10 days every 2 to 5 weeks.

36. A method according to any one of claims 1-28, wherein said compound is administered at least daily for a period of 2 to 10 days every 3 to 4 weeks.

37. A method according to any one of claims 1-28, wherein said compound is administered at least daily for 3 to 7 days every 2 to 5 weeks.

38. A method according to any one of claims 1-28, wherein said compound is administered at least daily 4 to 6 days every 2 to 5 weeks.

39. A compound having the following formula:



(I)

wherein:

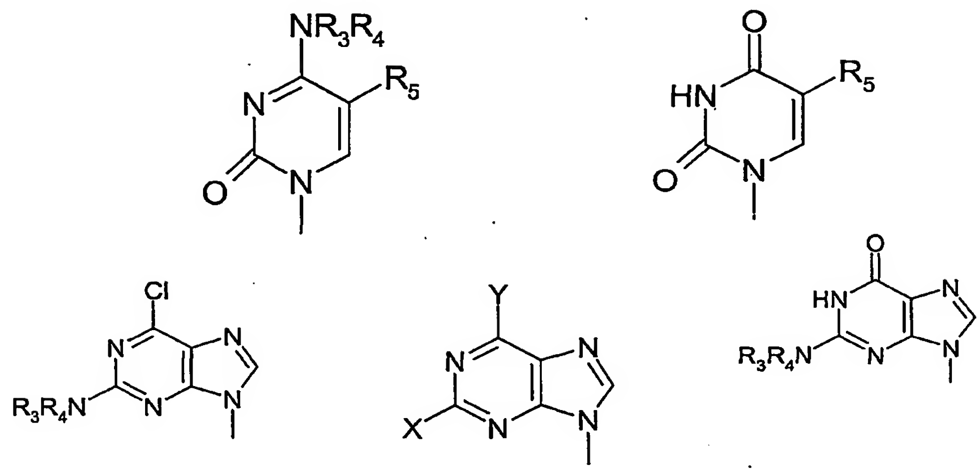
R_1 is H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NRH_6$; or an amino acid radical or dipeptide or tripeptide chain wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Met, Cys, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-20} alkyl, C_{2-}

$_{20}$ alkenyl, C_{6-10} aryl, C_{7-11} arylmethyl, C_{2-7} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R_2 is



R_3 and R_4 are in each case independently H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(O)OR_6$; $-C(O)NRH_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

R_6 is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R_7 is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} aryl, C_{5-10} heteroaromatic ring, C_{3-20} nonaromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4; or

a pharmaceutically acceptable salt thereof;

with the proviso that at least one of R_1, R_3 and R_4 is

C_{7-20} alkyl;

C_{7-20} alkenyl;

C_{6-10} aryl;

C_{5-10} heteroaromatic ring;

C_{4-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S;

$C(O)R_6$ in which R_6 is , C_{7-20} alkyl, C_{7-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{4-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S ;

$-C(O)OR_6$ in which R_6 is C_{7-20} alkyl, C_{7-20} alkenyl, C_{0-20} alkyl-C_{6-10} aryl, C_{0-20} alkyl-C_{5-10} heteroaromatic ring, C_{4-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; or

a dipeptide or tripeptide or mimetic thereof where the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which is optionally terminated by $-R_7$.

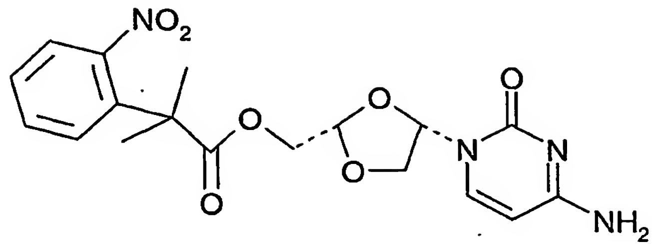
40. A method of treating a patient with cancer comprising
administering to said patient a prodrug form of troxacitabine, having a lipophilic structure to enhance entry of the prodrug into the cancer cells by passive diffusion, wherein said lipophilic structure is cleavable by cellular enzymes, thereby increasing the amount of troxacitabine within the cancer cells to a level greater than that allowable by administration of troxacitabine in nonprodrug form.

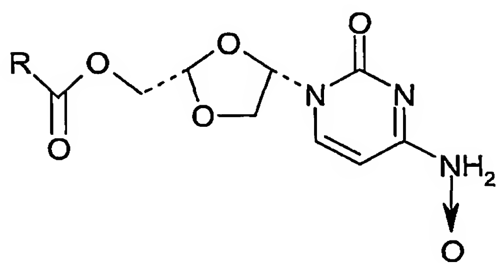
41. A method of treating a patient having cancer which is resistant to gemcitabine, cytarabine or both, comprising administering to said patient a troxacitabine derivative having a lipophilic structure which enhances the entry of the derivative into the cancer cell by the passive diffusion.

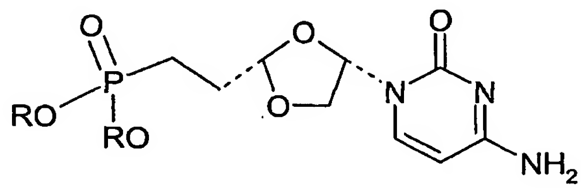
42. A method of treating a patient having cancer wherein the cancer cells are deficient in nucleoside or nucleobase transporter proteins, comprising administering to said patient a troxacitabine derivative having a lipophilic structure which enhances entry of the derivative into the cancer cells by passive diffusion.

43. A method according to claim 4, wherein said cancer cells are deficient in one or more nucleobase transporter proteins.

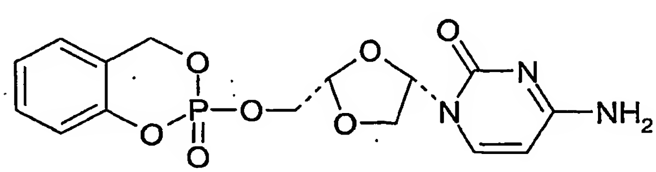
44. A method according to any one of claims 1-28, wherein the compound is of the formulas



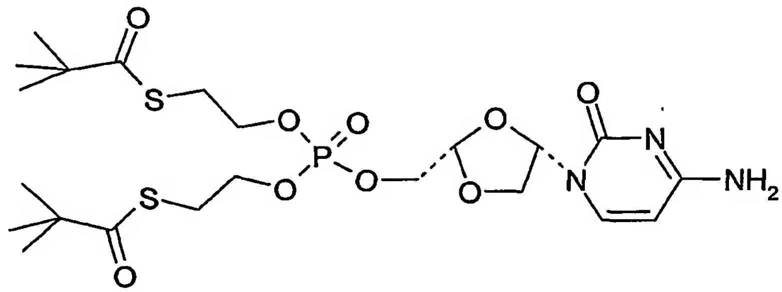




45. A method according to any one of claims 1 to 28 wherein the compound is of the formula



46. A method according to any one of claims 1 to 28, wherein the compound is of the formula



47. A method according to any one of claims 1 to 28, wherein the compound is selected from

4-HEXYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER (No. 191) ;

8-PHENYL-OCTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3]DIOXOLAN-4-YL)-2-OXO-1,2-DIHYDRO-PYRIMIDIN-4-YL]-AMIDE (No. 197) ;

8-PHENYL-OCTANOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER (No. 198) ;

4-PENTYL-BICYCLO[2.2.2]OCTANE-1-CARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER (No. 211) ;

4-PENTYL-CYCLOHEXANECARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL)-[1,3]DIOXOLAN-2-YLMETHYL ESTER (No. 240) or mixtures thereof.

48. Use of a compound of formula (I) as defined in any one of claims 1 to 38 or 43 to 47 in the manufacture of a medicament for treating cancer.

49. A pharmaceutical composition for treating cancer comprising a compound of formula (I) as defined in any one of claims 1 to 38 or 43 to 47, in association with a pharmaceutically acceptable carrier.

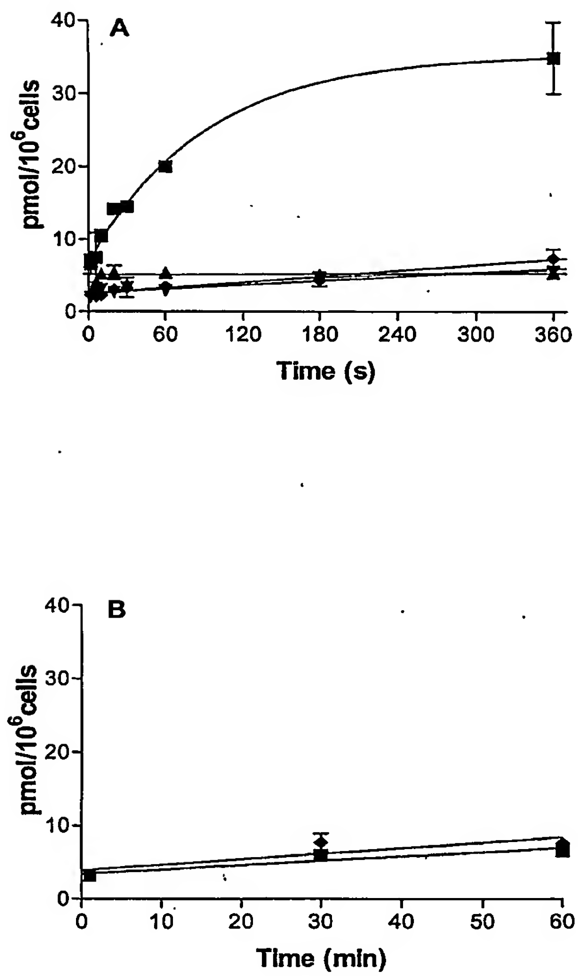

A
pmol/10^6cells
40
30
20
10
0
0
60
120
180
240
300
360
Time (s)
B
pmol/10^6cells
40
30
20
10
0
0
10
20
30
40
50
60
Time (min)

FIG. 1

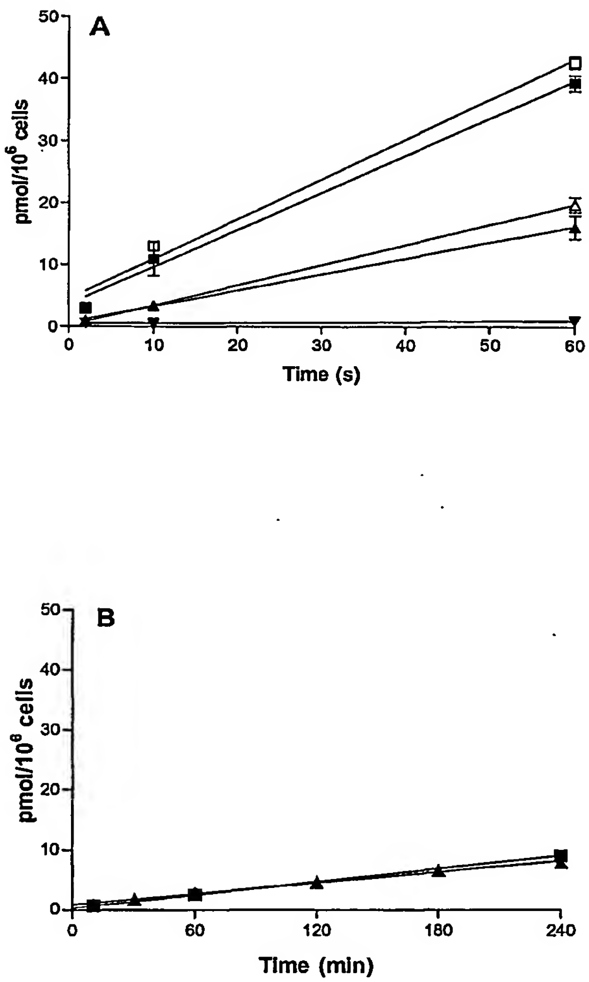

A
pmol/10^6 cells
0
10
20
30
40
50
60
Time (s)
B
pmol/10^6 cells
0
60
120
180
240
Time (min)

FIG. 2

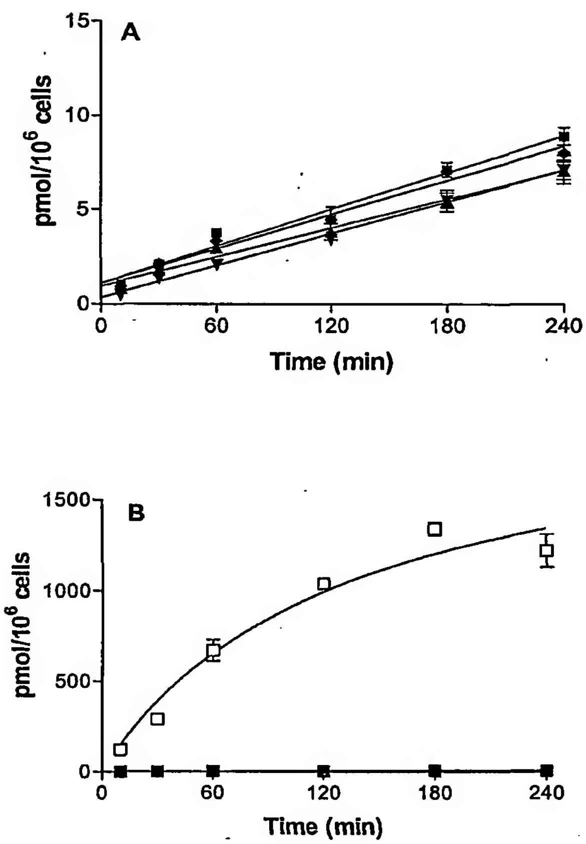
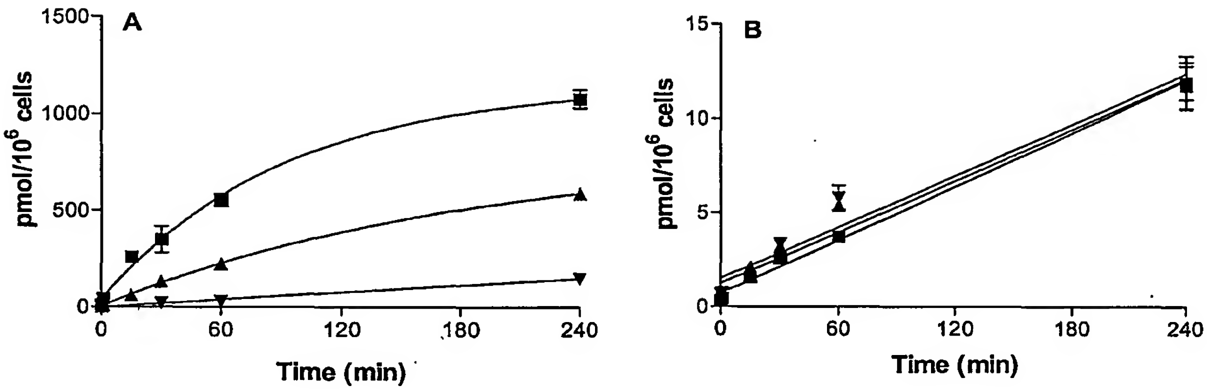

A
15
10
5
0
pmol/10^6 cells
0
60
120
180
240
Time (min)
B
1500
1000
500
0
pmol/10^6 cells
0
60
120
180
240
Time (min)

FIG. 3

hCNT1



hCNT2

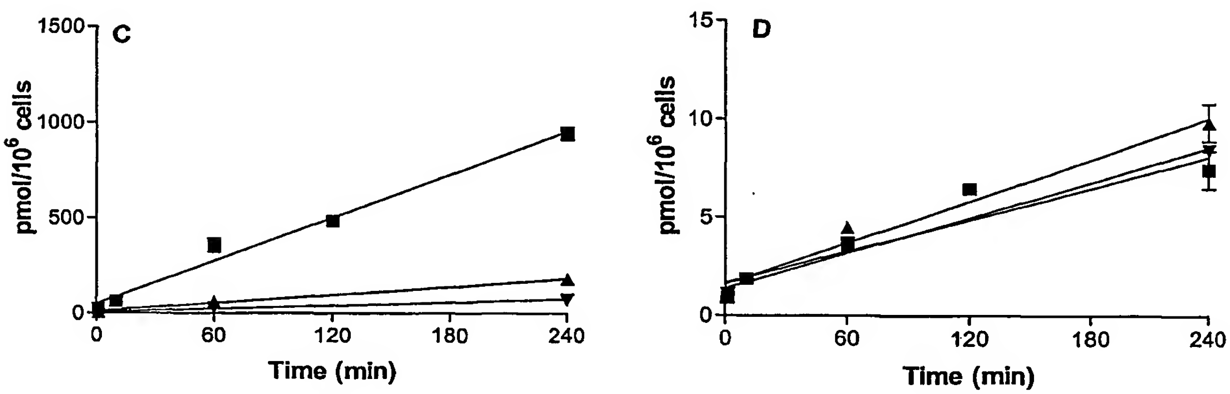


FIG. 4